STUDENT & PROFESSIONAL POSTER ABSTRACTS

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A GATHERING OF GLOBAL PERSPECTIVES

This year's Annual Meeting included over 120 posters delivered by students and professionals from around the globe who presented scientific developments related to topics addresses in this year's program. This supplement includes all poster abstracts delivered at this year's program.

Student Poster Winners *Congratulations!*

On Monday evening, DIA presented awards for the first, second, and third place student poster winners.

First Place: **Factors Influencing Quality Decision Making in Medicines Development and Regulatory Review**, Magdalena Bujar, MSc, University of Hertfordshire, United Kingdom

Second Place: **Pediatric Opioid Exposures and Poisonings: Prevalence and Characteristics**, Anisha Patel, MS, Virginia Commonwealth University School of Pharmacy

Third Place: **Identifying Symptoms and Functional Impact Reported by Persons with Multiple Sclerosis: A Qualitative Literature Review**, Mira Patel, MS, University of Arizona

M 01

A Gap Analysis of Marketers' Approach to Marketing of Pharmaceuticals and the Essential Functions of Marketing in Pharma 3.0

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Keywords: Pharma 3.0, pharmaceutical branding, pharmaceutical customer relationship management, pharmaceutical marketing innovation

Method: This study has been conducted by reviewing secondary literature i.e textbooks and research papers. The basic foundation is based on Kotler's and Blackette's textbooks. The gap analysis is based on the research work of Josef Bednarik, Z. Ladha, S. J. Kumar, Hebert Jack Rotfeld, Christian Gronoos, etc.

Objective: The objective of this paper is to analyse the gap between the original definition of marketing and the actual approach of current Pharmaceutical companies towards marketing their products, with respect to brand and customer relationship management in present scenario (Pharma 3.0).

Result: The preliminary results of this study which were obtained by reviewing the secondary literature state that for a long time, Pharmaceutical marketers have just focused on their drug molecule as a product. Major investment has been primarily in drug R&D process, rather than strengthening the brand image of their product or creating multi modal approach to manage the customer's relationship and loyalty well. The hypotheses that less emphasis has been laid over pharmaceutical brand management and that extensive focus has always been on developing and managing a pharmaceutical product / formulation / dosage form for the drug molecules is significantly true. The hypothesis that less efforts have been taken to cater to the same customer in different ways and means, so that he chooses his convenient way to get informed about the product without being disturbed with unnecessary information (as is the fundamental principle of marketing 3.0) leading to customer retention, is often overshadowed by a sales-oriented focus rather than customer friendly cost-effective consideration, holds significantly true. This states that the Pharmaceutical marketers lack in terms of marketing innovation and creativity. The product related functional or physical aspects, such as pharmaceutical dosage forms, bio availability, half life, delivery systems, etc. have only been the key areas of focus. Brand management, even for branded generics, has heavily suffered with respect to creating a robust image or brand personality to uniquely position itself in customers' minds. Brand management in pharma, with respect to most of the countries of the world except US and New Zealand where Direct to Consumer (DTC) Advertisements are banned have seen even less efforts with respect to pharmaceutical branding of prescription products. Since most of the discussions have been limited to physicians or pharmacists, pharma branding has just been considered as science, and not an art.

Conclusion: As R&D pipelines are slowly drying up and regulatory stringency has increased worldwide the pharmaceutical marketers no more have the luxury of just depending upon scientific or physical aspects of the drug molecules. The key tactic for the companies to survive and stand out in this cut throat competition in the pharmaceutical industry would be giving adequate attention and emphasis on managing their brands as well as customers and consumers, in more non conventional ways. This can be done only by being more creative and innovative with terms to designing robust brand positions along with designing better and smarter, customer centric multi modal approaches towards managing the customer relationships, which would lead to top of the mind recall as well as retention and loyalty. Along with managing the pharmaceutical products, it would now be imperative for the marketers to focus not only on creating brand salience and awareness, but also, to create such positive feelings and emotions in minds of the customers that they are able to get into a unique relationship with the brand which would in turn bring about loyalty and generate repeat prescriptions. This implies that, even if the current era of the Pharmaceutical Industry Pharma 3.0 aims at focusing on health outcomes (that are more consumer related) and not just benefits (associated with the physical aspects of the product), most of the pharmaceutical companies contradict this by following the exactly opposite principle. These companies would soon become susceptible to the threats of saturation or competition, if their age old marketing practice - of just pampering themselves with the physical/functional aspects of their product, and generating figures (revenues), is not upgraded to a more customer oriented approach. These companies are at the greatest risk of facing "marketing myopia", if they do not start looking at the pharmaceutical marketing as an art, with a creative, innovative and customer centric approach.

M 02

Factors Influencing Quality Decision Making in Medicines Development and Regulatory Review

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Keywords: Measurement instrument, pharmaceutical company, quality decision-making (QDM), regulatory agency

Method: The Quality of Decision-Making Orientation Scheme (QoDoS) consisting of 47 statements that measure organizational and individual decision-making approach and influences, was completed by 76 participants from regulatory agencies and companies. The data were analyzed using descriptive statistics.

Objective: To assess the quality of decision-making (QDM) by organizations and individuals in order to identify strengths and weaknesses, increase awareness of biases and best practices, and evaluate differences in decision-making behaviors between pharmaceutical companies and regulatory agencies.

Result: Thirty-eight individuals (male=27, female=11) from 12 agencies and 38 (male=22, female=16) from 23 companies participated in the study representing small and large organizations with varying levels of professional experience (range= 2-40 years).

QoDoS enables measurement against 10 key principles that underpin quality decision-making practices; having a systematic, structured approach to aid decision-making (consistent, predictable and timely); assigning clear roles and responsibilities (decision makers, advisors, contributors); assigning values and relative importance to decision criteria; evaluating both internal and external influences/biases; examining alternative solutions; considering uncertainty; re-evaluating as new information becomes available; performing impact analysis; ensuring transparency and providing a record trail; and effectively

communicating the basis of the decision. Assessment against these principles was evaluated across the 76 participants.

Applying a structured approach to decision-making, ensuring consistency, transparency and timeliness, were incorporated more at the individual level of decision-making (22% of participants indicating always) while this was only reflected at the organizational level for 7% of the participants.

An assessment of agency and company responses identified differences between the two stakeholders. Both groups considered evaluating the impact of the decisions as an important factor with agencies using a structured, systematic approach to decision-making more frequently than companies. Conversely, there was a general tendency for biases, due to politics, competitors or incentives, to have more impact on decision-making for companies compared to agencies. Whilst it was recognized that the science of decision-making is important, training in this area was rarely provided. Nevertheless, all responders from agencies and 92% from companies felt that they could make better decisions.

Conclusion: In the absence of a standardised valid instrument for measuring QDM in the pharmaceutical regulatory environment (Bujar et al. 2016), the QoDoS was developed using a standard approach for design and psychometric evaluation for measures of such nature (Donelan et al. 2015, 2016).

This study has demonstrated that some QDM practices, such as having a systematic, structured approach to aid decision-making, are applied to a greater extent at an individual level compared to that of organizational. This could relate to factors such as an individual being more accountable at a micro-level for the decisions they make as compared to the organization on a macro-level.

Whilst it was recognized that both agencies and companies felt that their decision-making could be improved, training in this area was rarely provided. Consequently, there is a need to utilise tools and frameworks to build quality into decision-making in association with other available approaches such as the implementation of benefit-risk assessment methodologies and good review/submission practices.

The findings of this study also demonstrate that the QoDoS has the ability to measure differences in decision-making and identify best practices between individuals and their organization as well as differences between companies and agencies. The overall benefit of assessing the quality of decision-making practices is to enable an increased awareness of biases and best practices but also provide the ability to measure change over time in order to determine the impact of improvement initiatives. In addition, the long-running use of quality systems for making decisions will generally give better outcomes for companies and agencies. Finally, such measurements of QDM will enable trust, consistency, transparency and timeliness to be built into critical decisions that ultimately improve patients' access to medicines.

M 03
Analysis of Postmarket Safety Labeling Changes: Comparison of Expedited Versus Standard NDA Approvals

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Keywords: Accelerated approval, expedited approval, fast-track, FDA, postmarket safety

Method: FDA approved drugs from 2007-2015 with expedited approval were reviewed for safety-related labeling changes using Drugs@FDA.gov. Rates of postmarket safety label changes for these drugs were compared to rates of postmarket safety label changes for a sample of standard approval drugs.

Objective: Recently, GAO reported FDA has not determined whether drugs approved via expedited process are associated with safety issues at rates different from drugs approved via standard processes. Our objective was to compare rates of labeling changes of drugs approved via expedited vs. standard mechanisms.

Result: A total of 119 drugs were identified as approved via the FDA's expedited processes: accelerated approval, breakthrough designation and fast track. Anti-infective and oncology medications were the largest categories of medication which were approved via expedited processes. Significant safety issues were defined as those requiring labeling changes. 25 drugs were approved via the FDA's accelerated approval process from 2007-2015; of these, 13 (52%) were found to have significant safety issues. 15 drugs were approved via the FDA's Breakthrough designation process from 2012-2015; of these, 6 (40%) were found to have significant safety issues. 79 drugs were approved via the FDA's Fast Track process from 1998-2015; of these 42 (53%) were found to have a post marketing safety issues that required a label change. In total, 61/119 (51.3%) of drugs that were approved through one of the FDA's accelerated approval processes were found to have a postmarket safety issue that required a labeling change. A sample of 119 drugs approved through the standard approval process were found to have 65/119 (54.6%) labeling changes due to postmarket safety issues. A comparative assessment of expedited vs standard approval drugs using Chi Square analysis revealed no statistically significant difference between the rate of safety issues between the two groups. Additionally, there were no statistically significant differences between rates of safety labeling changes for the three types of accelerated approvals studied in this analysis.

Conclusion: Drugs that were approved via an expedited process were not found to have significantly more postmarket safety issues as compared with drugs that were approved via the standard process. In fact, slightly less labeling changes were observed. The route of expedited approval also did not seem to affect the rate of safety labeling issues. The need for expedited drug approval to address unmet medical needs in the treatment of serious conditions must be balanced by a requirement that the benefits justify the risks.

M 04
The Key Issues of the Trial Subjects' Protection During First in Human and Bioequivalence Studies

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Keywords: Clinical site, informed consent, quality of life, trial subjects' protection

Method: Materials of the research were 3 surveys which included 3 questionnaires of 135 volunteers aged 18-45 years who participated in more than 1 CT and was involved in CT and BE studies during years 2014-2015 at Clinical and Diagnostics Center of National university of pharmacy.

Objective: At first in human (FIH) and bioequivalence studies healthy people are trials subjects. One of the main tasks for researcher is ensuring good health protection for them. The aim of our work was to formulate key issues of volunteers' protection and analyze their opinion about maintaining these issues.

Result: According to FDA and EMA guidelines; ICH GCP, Oviedo and CIOMS conventions the informed consent (IC) signing and health insurance are the most important aspects of trial subjects' protection. These aspects are mandatory requirements controlled by authorities. IC contains many specialized medical information which is hard to volunteers understanding. Special feature of clinical trials (CT) in Ukraine is obligatory HIV-test for volunteers especially in FIH studies. It's not regulatory requirement, but required by the trials' sponsors who justify this by repeatedly taken blood samples during FIH. So we decided to study volunteers' awareness in the main terms that could be used in IC, their opinion in obligatory HIV-test and quality of life (QoL).

The analysis of subjects' awareness in IC terms showed that 34% of them asked questions during reading, 91% were satisfied with answers. For evaluation of terms understanding the list of them was offered. Volunteers had to mark terms known for sure. According to the self-rating 39% of subjects know more than 90% of terms. For evaluation of the real knowledge level list of tests was offered. Tests showed that only 14% know more than 90% of terms, 11% know less than 50% of terms.

Assessment of opinion in obligatory HIV-test showed that 91% of subjects with FIH participation experience consider this test as reasonable. In survey was established that 9% of respondents don't know about the HIV transmission through unprotected sex so they are at risk of infection this way. 73% of subjects will pass test if it's not obligatory for participation. At the same time only 21% of people would participate in CT if one of them were HIV-positive.

The QoL evaluation showed that 90% of volunteers didn't change their social activity during CT. 93% of respondents had positive attitude about participation in FIH. 2% of subjects were afraid of health decreasing. After the end of FIH 79% of people noted they feel the same way as before the start.

Conclusion: The results showed that volunteers overestimate their awareness in special medical information in the IC form. This fact needs special attention by researchers. To increase the volunteers' safety with the help of IC trials' sponsors should pay more attention to its preparation. To ensure a higher level of volunteers understanding of terms given in IC an additional survey by the researcher with followed explaining of unclear information; visual aids for better perception of specialized information could be used. Analysis of the research participants' awareness regarding issues related to HIV showed that certain percentage of volunteers don't have sufficient information on infection pathways and find true some false public opinions regarding HIV. It is very important to understand whether it has an effect on mental health of volunteers during the HIV-test is held. Overall, most participants of CT are positive about this procedure and would like to receive an additional information on this issue in preparing, holding and obtaining test results. Assessment of QoL in bioequivalence study at our clinical site suggested a general well-being and satisfaction by the parties of human life, which has an impact on human health. This is very important because during CT volunteers stay at clinical site from 3 to 14 days, and the same amount after the wash-out period. Indirectly this indicates a high level of work quality of clinical site staff because their work had no negative medical, mental or emotional impact on volunteers. The presence of participants who were afraid of ill health during participation in CT, suggests the need for psychological support and extra attention from researchers to such volunteers at various stages of the study (screening, hospitalization day and etc.). Summarizing the results, we can conclude about the need to improve healthy volunteers' and patients' protection involved in CT and bioequivalence studies.

M 06

Analysis of Off-Patent Pharmaceutical Price Increases: 2013-2016

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Keywords: Drug Competition, Drug Pricing, FDA, Generic Market, Off-patent

Method: Price changes from 2013-2016 for off-patent drugs were accessed from Micromedex and RedBook databases. The increases were classified and analyzed for their potential impact on patient care. Various regulatory and legislative solutions proposed to diminish this evolving problem are presented.

Objective: The objective of this study is to investigate the magnitude of price increases for off-patent pharmaceuticals over the last 3 years. Various proposed regulatory and legislative solutions are summarized and evaluated.

Result: The emerging issue of off-patent pharmaceutical price hikes has been a major concern headlining the media and causing reasonable debates in Congress. The price increases of 266 off-patent pharmaceuticals were evaluated. Since 2013, increases by at least one manufacturer were noted in 151/266 (57%). Increases of > 200% since 2013 were noted in 88/266 (33%). Several critical care medications such as digoxin, sodium nitroprusside and isoproterenol had increases in excess of 200%. This recent change has negatively impacted many hospitals that use these drugs on a daily basis. Several categories of medications were involved in a large number of increases: powders, solutions, injectable of diuretics, antibacterial, ACE inhibitors and anesthetic drugs. Our findings showed, that the same manufacturers distributed most of the price-increased drugs. Approximately, 25/266 (9.4%) of these drugs were sole source generic drugs, meaning there was no price competition at all. A notable example is ethacrynic acid, which experienced a percent change 14 times by its sole manufacturer within a short span of 2½ years. In addition, changes in acquisition costs for some of the generic off-patent drugs like Captopril, doxazosin and fluconazole were reviewed and analyzed with significant percent changes in National Average Drug Acquisition Cost (NADAC) exceeding 1000% within a year period.

We examined several possible regulatory and legislative alternatives currently under consideration to address the issue of rising generic medication costs, e.g. bulk compounding in accordance with the 2013 Compounding Quality Act, temporary importation of foreign approved drugs, expedited Abbreviated New Drug Application (ANDA) review for off-patent drugs not subject to competition, and changes to Hatch-Waxman exclusivity provisions.

Conclusion: As the gatekeepers of pharmaceuticals, the Food and Drug Administration (FDA) has been urged to become more involved in the accessibility and affordability of essential drugs entering the market, even after their patents have expired. In a free market, prices of pharmaceuticals are not regulated by law or the FDA. Off-Patent drugs have lost their legal monopoly, yet their prices have increased over the last three years. One reason for price drug increase is the lack of competition. Our analysis revealed that many common medications widely used in practice today have increased in price over the last 3 years. FDA and other policy makers have an essential role in pursuing policies and strategies to ensure patient access and affordability to off-patent pharmaceuticals to reduce both morbidity and mortality.

M 07
Synergetic Prevention of Sudden Death by ACEI, Statin and Gliflozin in Type 2 Diabetes: A Simulation Study

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Keywords: Innovative tool, simulation, sudden death, type 2 diabetes, virtual realistic population

Method: We developed a SCD risk score for T2D from 7 RCTs; estimated risk reductions on SCD by each of the tri-therapy through related meta-analyses and trials; finally, we integrated these results on a VRP generated from real French cohorts with risk-based and different therapeutic strategies scenarios.

Objective: Sudden cardiac death (SCD) is the first cause of cardiovascular deaths in type 2 diabetes (T2D). ACEI, statin and recently empagliflozin have shown efficiency for SCD prevention in T2D. We estimated the public health impact of this tri-therapy on SCD in a diabetic virtual realistic population (VRP).

Result: A predictive SCD score was built from 30560 individual patient data of 7 randomized controlled trials (INDANA database and DIABHYCAR trial), using Cox regression proportional hazards model, censored at 5-year period. The significant risk factors were age (HR 1.07, CI 1.06-1.09, p <1e-16 for 1year), male sex (HR 2.32, CI 1.65-3.26, p <1e-6), total cholesterol level (HR 1.13, CI 1.02-1.26, p= 0.02), systolic blood pressure (HR 1.011, CI 1.003-1.019, p <0.005), smoking status (HR 1.84, CI 1.40-2.41, p <1e-5), history of myocardial infarction (HR 2.15, CI 1.47-3.13, p <7e-5), and diabetes mellitus status (HR 2.93, CI 1.80-4.76, p =1.5e-5). Important interaction between diabetes status and sex was found, indicating that in diabetic patients, both sexes might have comparable risks of SCD. Area under the receiver-operating characteristics (ROC) curve of the model was of 70%. A clinical scoring system was also established for simple assessment of SCD risk. Our model was applicable for patients with T2D and/or hypertension and was the first score for SCD prediction in cardiovascular primary prevention.

Latest related meta-analyses and trial indicated significant relative risks (RRs) of 90%, 85% and 69% on SCD risk in T2D by statin (Rahimi et al.2012), ACEI (Benoit et al. 2014) and gliflozin (EMPAREG-OUTCOME trial, 2015), respectively. Supposing no interaction existing between these drugs, the relative risk of the tri-therapy was RR = 0.90 * 0.85 * 0.69 = 0.53.

A French diabetic RVP of 176 187, aged from 40 to 75 was generated from a 8 995-patient sample, giving an median of SCD risk of 1.7% at a 5-year time horizon. A simulation of public health impact on this platform estimated the numbers needed to treat (NNTs) at 221 people for the whole population and at 105 among individuals of the highest 10% predicted SCD risk, if treated simultaneously this tri-therapy for one year. The corresponding untreated risks of SD were of 1.9% and 4.0% respectively.

Conclusion: For the first time, we developed a SCD risk score for primary prevention (also applicable for those with diabetes and/or hypertension). Our score confirmed common risk factors as suggested by classical scorer (cardiovascular Framingham score). As well, we proposed an innovative approach to estimate impact of various drug strategies on a VRP and approved its feasibility by a simulation in T2D by the statin-ACEI-gliflozin tri-therapy. Such co-prescription appears to prevent 1 SCD in 221 treated diabetic patients in 1 year. However, interaction between concerned these drugs should be further verified. A study to elucidate this point by our team suggested no important interactions could have significant impact on their combination.

In general, we suggested the OPTI-VRP (OPTImize therapeutic strategies on a Virtual Realistic Population) approach to simulate public health impact (PHI) step by step:

1. O (Outcome): Choose outcome(s) of interest
2. P (Population): Define the population on which optimizing PHI
3. T (Treatment): Choose treatments of interest
4. I (Integration): Generate the targeted VRP and integrate available information obtained from OPT (the three items above) to simulate PHI.

This OPTI-VRP is a multi-component approach which allows accurate fitting to the characteristics of the particular population of interest. In perspectives, we could: i. Re-use VRP for other objectives, such as validation of risk scores; ii. Enrich the approach by external data/information source; and iii. Integrate various constraints of optimization, eg. cost, utility, side effects, etc.

Our OPTI-VRP approach that gathers effect models (via meta-analyses and risk scores) and VRP simulation provides a clinical powerful tool. This could help valuing each evidence-based component, better transposing clinical trial results into practice, facilitating clinical decision in both public health and at individual levels, on both medical and economic aspects.

M 08
Formulary Processes of Major Countries

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Keywords: Drug formulary management, public drug funding

Method: A systematic review was done in October 2015 on public-funded drug formulary management practices of various countries. Besides PubMed and Scopus, individual organizations' websites were explored. The same keywords ('drug formulary', 'medicine list', 'management', 'maintenance') were used.

Objective: To compare the public drug formulary processes of major healthcare systems.

Result: The public formulary processes of four countries in different continents were selected. The formulary governing body, drug listing initiation, pharmacoeconomics technical assessment, funding selection criteria, and committee decision transparency were compared.

For US, which depends largely on varied insurance plans, the Medicare prescription drug coverage plans managed by Centers for Medicare and Medicaid Services, was selected for ease of comparison. The Pharmacy and Therapeutics Committee reviews and decides on new drug inclusions for various health system pharmacies. Selection criteria include appropriateness, safety, cost-effectiveness, and efficacy. The Medicare Parts C and D provide some degree of prescription drug coverage, but these are constrained by individual providers.

In United Kingdom, the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee (TAC) makes recommendations to the National Health Service (NHS) on selection of drug for funding. The NICE TAC evaluates drugs with help from Evidence Review Groups and Assessment Groups commissioned by NHS National Institute for Health Research. Non-health factors are also considered along with comparators available.

The Australian Pharmaceutical Benefits Advisory Committee (PBAC) recommends to the Minister for Health on Pharmaceutical Benefits Scheme. The PBAC assesses new drugs with help from Drug Utilization Subcommittee and Economics Subcommittee. The drugs must be approved by Therapeutic Goods Administration for quality, safety, and efficacy are already ensured.

In Singapore, the Drug Advisory Committee (DAC) recommends to the Ministry of Health on Standard Drug Lists and Medication Assistance Fund drugs, which are covered by means-tested subsidies. The Pharmacoeconomics and Drug Utilization Unit provides technical and secretarial support to the DAC. As with the other countries, the preference is for drugs which are proven efficacious and cost-effective.

Conclusion: Each country has a formulary management process unique to its social histories and policy-makers' believes. There is no 'one size fits all' model. While comparing various formulary strategies gives an overview on the focus of each healthcare system; developing countries attempting healthcare reform need to consider their own developmental stages and public expectations of healthcare funding, without blindly adopting any model in formulary management.

M 09

Evaluation and Characterization of Health Economics and Outcomes Research in SAARC Nations

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Keywords: Cost Analysis, India, pharmacoeconomics, quality of Life

Method: Studies published in English language between 1990 and 2015 were retrieved from Medline databases using relevant search strategies. Studies were independently reviewed as per Cochrane methodology and information on the type of research and outcomes were extracted. Quality of reporting was assessed.

Objective: To identify, evaluate and characterize the variety, quality, and intent of the health economics and outcomes research studies being conducted in SAARC (South Asian Association for Regional Cooperation) nations.

Result: Of the 2638 studies screened from eight SAARC nations, a total of 179 were included for review. (India=140; Bangladesh=12; Sri Lanka=08; Pakistan= 07; Afghanistan=05; Nepal= 04; Bhutan=02; Maldives=01) The broad study categories were cost-effectiveness analyses [CEA=76 studies], cost analyses [35 studies], and burden of illness [BOI=26 studies]. The outcomes evaluated were direct costs, indirect costs, and incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALYs), and disability-adjusted life years (DALYs). Cost of medicines, consultation and hospital charges, and monitoring costs were assessed as direct medical costs along with non-direct medical costs such as travel and food for patients and caregivers. The components of indirect costs were loss of incocme of patients and caregivers and loss of productivity. Quality of life (QoL) was assessed in 48 studies. The most commonly used instrument for assessing QoL was the WHo-Quality of Life BREF (WHOQOL-BREF) questionnaire (76%). The Quality of Health Economic Studies (QHES) score was used for quality assessment of full economic studies [44 studies]. The mean QHES score was 43.76.

Conclusion: This review identifies various patterns of health economic studies in eight SAARC nations. The quality of economic evaluation studies for heath care in India, Bangladesh, Sri Lanka, Pakistan, Afghanistan, Nepal, Bhutam and Maldives needs improvement. There is a need to generate capacity of researchers to undertake quality economic evaluations as well as an orientation of the policy makers so that there is demand for such studies as well as a scope for its use in policy making.

M 10

Factors That Affect Market Share of Biosimilars Against Reference Biologics

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Keywords: Biological products, biopharmaceuticals, biosimilar, pharmacy

Method: For this study, we reviewed literature of biosimilars and the respective reference biologic product in the current global drug market. The outlook and drugs were assessed by product makeup, therapeutic classes and indications, healthcare expenditures, regulatory status, and geographical location.

Objective: The objective of this study to evaluate existing and possible new factors of the current healthcare system and pharmacoeconomics landscape for analyzing market share outlook of biosimilars among pharmaceutical companies, in relation to the innovator biologic products.

Result: The biosimilars landscape is focused on recombinant non-glycosylated proteins (filgrastim, insulin, interferons), glycosylated proteins (erythropoietin, monoclonal antibodies, and peptides (calcitonin, glucagon); the application of these agents and their reference biologics are mostly used and applied in oncology and blood disorders. In the European market, Granulocyte-colony stimulating factor (G-CSFs) had an increase of biosimilar market share from 1% in 2008 to 60% in 2013 against the reference biologic product. Erythropoietin-stimulating agents (ESAs) increased from 3% in 2008 to 25% in 2013 against the reference biologic product. In the US, the first biosimilar was only approved in March 2015, with many products in pipeline from a multitude of market players. Biosimilars is projected to account for 4-10% of the biologics market total by 2020, which is dependent on regulatory approval. The growing demand of biosimilars to decrease healthcare expenditures is being fueled by expiring brand patents, reducing

patient out-of-pocket costs, increasing alternative, interchangeable drug regimens and therapeutic cost-effectiveness. With the rising incidences of various diseases like rheumatoid arthritis, blood disorders, and numerous cancers, statistically and clinically significant outcomes in ongoing clinical trials of biosimilars in comparison to placebo is to be noted. Factors affecting a decrease in market share of biosimilars include drug complexities, expensive manufacturing costs, and strict regulatory approvals and processes. Biologic reference products have not always been priced above biosimilars. Between 2005 and 2013, the level of price erosion has been gradual for epoetin alfa, epoeitin beta, filgrastim, and lenograstim, in comparison to the respective biosimilars. The global biosimilars market is expected to increase to $6.22 billion by 2020, with a compound annual growth rate (CAGR) of 22.1% from 2015 to 2020.

Conclusion: The emergence and innovative implementation of biosimilars in relation to pharmacoeconomics will affect the market share of existing drug products. New research and business development endeavors, approval pathways and dispensing legislations, treatment alternatives, patient safety and effectiveness monitoring/guidelines, costs and reimbursements are all factors in the biosimilars market against reference biologics. While patent drugs are expiring, biosimilars approval and alternative use will decrease payer costs, which affects therapeutic cost-effectiveness. Neither a generic nor a novelty brand drug, biosimilars are gaining increasing use and affecting healthcare systems and healthcare economics worldwide. The application of biosimilars in diseases like cancer, diabetes, rheumatoid arthritis, multiple sclerosis, and other serious conditions motivates more biosimilars to be implemented in the market, especially when the agents provide a cheaper, effective and safe alternative. However, pharmaceutical companies are faced with drug complexities, expensive manufacturing costs, and strict regulatory approvals and processes, which can hinder market share outlooks when comparing biosimilars to reference biologic products. Therefore, expansions of pharmaceutical companies such as partnerships, joint ventures, and agreements have strengthened market players and their portfolios. Many countries in Europe have already approved biosimilars and they are currently dominating the global biosimilars market; the US and the Asia-Pacific will soon experience more biosimilar products. This is due to the developing infrastructure of healthcare, increasing patient population, and growing investments and funding for the advancement of biosimilars. Biosimilars will affect our lives, and the lives of our patients both in the short- and long-term. The worldwide healthcare system and pharmacoeconomics will continue to adapt as different biosimilars become available.

M 11

Best Practices for the Design and Dissemination of Patient Medication Information: A Systematic Review

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Keywords: Healthcare communication, patient engagement, prescription labeling

Method: Articles were selected from three online databases (PubMed, EMBASE, CINAHL) and screened by three independent coders. Manuscripts were eligible if they were 1) English-language, 2) conducted in the US, UK or Australia and 2) provided evidence on how to improve prescription drug labeling practices.

Objective: Our objective is to present findings from a recent, systematic review of evidence supporting best practices for the presentation of quantitative, qualitative and descriptive information pertaining to the use and precautions associated with prescribed medications.

Result: A total of 14,285 articles were returned from the primary search. Following the title review, 190 articles remained. The abstract review eliminated an additional 94 articles. After reviewing the 96 remaining articles, 67were selected for data abstraction. Review of the selected articles revealed various themes related to best practices for 1) health literacy and the use of plain language, 2) labeling format and organization, 3) numerical content for representation of empirical results, 4) use of pictograms and illustrations, 5) shared decision making, and 6) modes of dissemination. Common outcomes of interest included satisfaction, knowledge and comprehension, retention of information, patient preference, and behavior (i.e. adherence, medication errors). To the latter, outcomes related to demonstrated or actual use of prescribed medications were less prevalent. A quality rating review revealed the majority of studies were labeled less than 'good' in terms of methodological quality, with less than half utilizing a randomized controlled design. Very few studies engaged patients' perspectives in the design of these educational materials, or at least provided minimal detail on how patient involvement was operationalized.

Conclusion: The present body of literature demonstrating evidence of best practices for medication communication is surprisingly limited, either in terms of breadth of research and definitive findings, or methodological rigor. The evidence is strongest in terms of using plain language and patient-friendly content to convey risks and benefits to patients, including the use of explicit, while parsimonious text. Evidence was also moderately strong for format and organization of written labeling materials, while less so for other multimedia options. However, findings here were variable and not cohesive. Studies examining quantitative information presentation formats were prominent but suffered from methodological weaknesses, including less generalizable samples. Beyond a call to action for more definitive studies to inform practice standards for industry and others on how to best communicate medication information to consumers, we review a sizable evidence base and share thoughts on what can be solidified for recommendations now, and how to narrow future research objectives to best fill needed gaps. Importantly, future studies should also consider engaging patients earlier in the design process to optimize comprehensibility and use of patient medication information.

M 12

Impact of Smartphone Use in Health Care by Providing Smartphones to Patients: A Systematic Review

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Keywords: Chronic diseases, mobile health, smartphones

Method: A systematic review was conducted regarding smartphone use published between 2005-2015 using PubMed, Medline, Cinahl Plus and Cochrane Library. Cochrane Risk of Bias Tool was used to assess risk of bias and Covidence was used to facilitate the summary of selected articles.

Objective: The objective of this study was to explore the literature regarding patient use of smartphones to improve health outcomes, to explore the idea of health plan purchase of smartphones for patients, and to discuss the costs associated with purchase of smartphones to improve health outcomes.

Result: Based on the inclusion criteria applied, search yielded a total of 42 articles. All of the articles were RCTs. Studies show that patient use of smartphones is widespread with a projected increase of over 27 million smartphone users in the US Several examples were identified and focused on three key areas: disease and medication management, personal fitness and wellness and remote monitoring. Studies included managing these chronic diseases: diabetes, HIV, hypertension, heart failure, chronic pain, substance abuse and mental health diseases. Smartphones that allowed remote monitoring had the greatest impact on avoidable costs by reducing hospitalization and emergency room visits. The majority of studies (72%) related to disease management showed a positive improvement in clinical outcomes. Smartphones that featured mobile coaching and medication reminders had high patient satisfaction and increased medication adherence. While there were few articles retrieved that directly addressed health plan purchase of smartphones for patients, one of the three articles mentioned health plan deployment of apps in targeted population health programs. For example, Kaiser's My Health Manager is used by 3 million members. If 10% of those members own a smartphone, that represents 300,000 patients that benefit. While the economic impact can be considered significant, none of the studies identified thoroughly examined the associated costs with provision of smartphones to patients.

Conclusion: The smartphone is one of the most dynamic trends in communication. Smartphones can be used to collect data directly from patients and subjects for clinical trial participation. Self-management and remote monitoring of patients via smartphones are becoming viable solutions for management of chronic conditions. According to the Wolters Kluwer Health 2013 Physician Outlook Survey, eight in 10 physicians use Smartphones in their daily practice and six in 10 use tablets. Over half (55%) use both smartphones and tablets in their daily practice. The top use of smartphones is for accessing drug information while tablets are used most to access medical research. Real time data can be gathered which has the potential to help both patients and providers. Due to the lack of studies found regarding cost, future research is warranted.

M 14

Pediatric Opiod Exposures and Poisonings: Prevalence and Characteristics

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Keywords: Children/pediatric, National Poison Data System (NPDS), opioid exposures, opioid poisonings

Method: We examined closed cases of children < 18 years with a suspected opioid exposure in the National Poison Data System (NPDS). Opioid exposures were characterized based on clinical factors and socio-demographics. Prevalence rates were standardized by the age-adjusted US Census population estimates.

Objective: Among different drugs involved in pediatric exposures, opioids are an important class due to a rise in their medical and nonmedical use. This study examined the prevalence and characteristics of pediatric opioid exposures and poisonings.

Result: We identified 83,418 children exposed to an opioid over the five-year period (January 1, 2010 to December 31, 2014). More than half of them experienced poisoning i.e., an exposure that resulted in clinical effects. About 61.2% of these children were <= 5 years old, over 90% of exposures occurred at home and involved ingestion. Nearly half of the exposures involved a single-substance opioid, the majority involving tramadol, oxycodone, buprenorphine, codeine or hydrocodone. About 73.4% of exposures were unintentional (i.e., accidental) and 18.8% resulted from a therapeutic error. One-fourth of exposures involved co-ingestants or multiple opioid and non-opioid products. Nearly 33.4% of the children had at least one related clinical effect including neurological, cardiac and respiratory effects, 11% had a moderate-to-severe outcome (including death) and 8.5% were admitted to critical care following an opioid exposure. About 6.4% were treated with naloxone. The total prevalence rate of opioid exposures was found to be 22.6 per 100,000 children. The annual prevalence rate of opioid exposures decreased from 2010 to 2014 (25.5 to 20 per 100,000 children, respectively). The prevalence rate was higher among children <= 5 years (42.4 per 100,000 children) compared to those 6 to 12 years and 13 to 17 years (6.1 and 22.2 per 100,000 children, respectively). Generalized linear mixed model showed a statistically significant yearly trend. The number of opioid exposures decreased from 2010 to 2014 after adjusting for random effects of states. In multivariable regression, older age, non-accidental intent, and involvement of a single substance opioid, rather than a combination product, were found to be significantly associated with severe outcome (which included moderate outcome, major outcome or death), following an opioid exposure in children ($p<0.05$).

Conclusion: Pediatric opioid exposures and poisonings still continue to occur. While the prevalence of pediatric opioid exposures and poisonings has declined over time, the magnitude of the annual decreases has been low. Our results suggest that opioid exposures are more prevalent in younger children and are mostly unintentional in nature. Younger children may gain access to opioids belonging to others at home. This can lead to an opioid exposure and poisoning, resulting in negative health outcomes. Development of educational efforts and targeted prevention strategies that are age-specific is warranted. Further analyses will identify the economic burden associated with opioid exposures and poisonings in children.

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M 15

Identifying Symptoms and Functional Impact Reported by Persons with Multiple Sclerosis: A Qualitative Literature Review

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Keywords: Multiple sclerosis, patient-reported outcomes, systematic literature review

Method: Searches were conducted in MEDLINE and PsycINFO using a pre-determined search strategy. Abstracts were included for full-text review if they met the following criteria: (1) referenced the use of

qualitative methods, and (2) identified MS symptoms and functional impact from a patient's perspective.

Objective: A systematic literature review was conducted to identify patient-reported symptoms and functional impact of multiple sclerosis (MS) to inform selection of content/concepts that should be included in patient-reported outcome (PRO) measures used to support efficacy endpoints in MS treatment trials.

Result: Sixteen articles identified key symptoms and/or functional impact relating to the patients' experience with MS. Standard qualitative methods of face-to-face/telephone interviews (n=10), focus groups (n=5), and written, open-ended questions (n=1) were used to obtain data in the reviewed studies. Six studies indicated the MS subtype(s) of the study population: relapsing-remitting MS (n=6); primary-progressive MS (n=3); secondary-progressive MS (n=4). Twelve major symptoms (as acknowledged by the National MS Society as "more common" symptoms) were identified within the studies: depression (n=7); pain (n=9); numbness/tingling (n=9); sexual dysfunction (n=5); fatigue (n=14); spasticity (n=4); lower extremity impairment/walking impairment (n=13); upper extremity impairment (n=5); bowel/bladder problems (n=6); vision problems (n=7); dizziness/vertigo (n=2); cognitive impairments (n=7). Other less frequently observed symptoms such as sleeping problems, headaches, speech problems, heat intolerance, and emotional problems were indicated. Four main domains in relation to functional impact due to MS were reported: social life (n=9); work life (n=6); relationships and family (n=12); independence (n=6).

Conclusion: The key symptoms reported by patients in the published studies were concordant with those identified by the National MS Society. Many of the symptoms identified were reported as co-occurring (e.g., spasticity and pain) causing further distress according to patients. In addition, these symptoms impacted patients in their daily lives which resulted in their inability to participate in social and work activities, live independently, and optimally maintain relationships. These findings provide a framework to assist in the development or selection of PRO instruments used for assessing symptoms and functional impact as part of an efficacy endpoint strategy for clinical trials in MS patients. Additional qualitative research will be needed to determine whether the symptoms and functional impacts differ based on patients' specific MS subtype. This review was conducted for and supported by the Patient-Reported Outcome Consortium's Multiple Sclerosis Working Group at the Critical Path Institute.

M 16

Direct-to-Consumer Television Marketing of Oncology Products in the US

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Keywords: Direct-to-consumer marketing (DTCM), hematology, oncology, television commercials

Method: We analyzed the following commercials: pegfilgrastrim, raloxifene, nivolumab, and sipuleucel-T. We looked at average length in seconds and analyzed these components of each commercial: indication; adverse effects, warnings and precautions, and contraindications stated; and marketing strategy.

Objective: The objective of this poster is to analyze the only four oncology direct-to-consumer marketing commercials observed after 2010 to determine the tactics utilized to communicate drug information to a specific patient population.

Result: The preliminary results of the comparisons indicate that while the commercials themselves vary in disseminating information to their target population, they all ranged from 60-90 seconds in length. Adverse events and warnings were heavily emphasized as they were the lengthiest portion of each commercial, accounting for 15-30 seconds. However, potential benefits and patient recommendations to ask their physician about the product were both allotted 3-5 seconds and 3 seconds, respectively, in the beginning and end of the commercials. Images, messages, and emotions that were present in each commercial were identified, such as family, patient self-identification, womanhood, and manhood. Endpoints of focus in the commercials were primarily extending life, reducing the risk of malignancy and reducing complications associated with the treatment of said malignancy.

Conclusion: While direct-to-consumer marketing of oncology products is rare, the commercials analyzed in this study focused on facilitating a dialogue between a patient and their physician to talk about the potential benefit a specific medication could have for said patient. All the commercials were similar in structure and the timeline of the information presented. However, they differed significantly in images and messages based on their unique target patient population. Overall, the end goal of these advertisements focused on educating the general public about the disease state and increasing communication with health care providers.

M 17

Unique Pharmaceutical Market and Pricing System in Japan: Suggestions to Global Pharma for Effective Market Penetration

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Keywords: Drug pricing system, Japanese pharmaceutical market, marketing strategy, R&D, regulatory science

Method: The data set for this study was created from the IMS Market Database. Uni- and multivariate logistic regression analyses, a simple linear regression model and an economic model based on the drug price elasticity were applied in this research.

Objective: The main objective is to reveal profiles of the Japanese market including pricing systems, which will be useful for those pharma companies that aim to join Japanese market, based on the analyses between the top-selling drugs in the Japanese market and those in the US, UK, France, and Germany.

Result: More cardiovascular and less central nervous system (CNS) and oncology drugs were ranked among the top 100 best-selling drugs in the Japanese market, which is different from the market in other developed countries. Further, generic drugs have eroded, especially in therapeutic areas with no assured benefits in the global market, such as cardiovascular drugs. A significant difference was confirmed in the number of the cardiovascular drugs in Japan. R2 values were calculated between sales by therapeutic areas and country, suggesting that the extent of transition to a global market were in the following order: United States > United Kingdom > Germany > France > Japan. Overall, the Japanese market was unique in that drugs in CNS

and oncology were not highly profitable compared with the other countries. However, it was confirmed that Japanese unique pricing system "Reward Premiums for the promotion of innovative drug discovery and resolution of off-label use issue, etc" encouraged the development of new drugs in neurology, oncology and orphan diseases. The following factors were significantly related to receiving a reward premium from this incentive system between 2010 and 2014 from the odds ratios calculated by logit regressions: a more recent launch, a global promotional company, and an orphan drug designation. Cardiovascular drugs were less likely to receive rewards, whereas drugs acting on the CNS and anti-cancer agents were significant contributing factors to receive reward premiums. The reward system positively affected drug sales in specific therapeutic areas, including neuroscience and oncology, as well as the quantity sold of neuroscience-related drugs, indicating that it has been working in accordance with its aims of promoting the development of new drugs.

Conclusion: Current Japanese pharmaceutical market has unique characteristics among developed countries; the significant number of cardiovascular drugs is available in Japan. Recently in Japan, development has primarily focused on "Oncology" and "Neurology" drugs through unique pricing system. Therefore, the Japanese market is expected to catch up with overseas markets in the near future, suggesting that the development of innovative CNS and oncology drugs is highly important for both Japanese and global pharmaceutical companies.

Another result of this study is that the drugs in neuroscience and oncology have a significant positive relation to the reward premiums. In addition, drugs sold by a global pharmaceutical company and designated orphan drugs, significantly contributed to the rewards as well. However, cardiovascular drugs have a significant negative relation to the rewards indicating that this unique incentive program has been encouraging the development of drugs which meet the high medical needs in specific therapeutic areas such as neurology and oncology.

This study also examined the effects of this premium rewards system on both drug sales and quantity of drugs sold. In particular, this system had a positive effect on drugs in neuroscience- and oncology-related areas, suggesting that it has been working in accordance with its original aims of promoting the development of innovative drugs.

In conclusion, this research revealed the following characteristics in Japanese market: 1) More cardiovascular and less CNS and oncology drugs were ranked among the best-selling drugs in the Japanese market; and 2) the unique incentive system has been working well in Japan to encourage the R&D of neurology, oncology, and orphan disease drugs; and 3) the Japanese market will rival overseas markets in the near future.

Authors believe that these analyses results would be useful for those global pharma companies that aim to join Japanese market and achieve/maximize profits in Japan.

M 19

Adherence to Guideline on Use of Analgesics in Patients with First Myocardial Infarction Event: A Stepped-Care Approach

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Keywords: Analgesic drugs, Cardiovascular events, Guideline adherence, stepped-care approach

Method: Using national health insurance sharing service cohort database, patients with first myocardial infarction between 2008 and 2011 included and guideline adherence was assessed with 2-year follow up. With propensity score matching, Kaplan-Meier curve and Cox regression analyses were conducted.

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Objective: The study aims were to assess adherence to the American Heart Association guideline on the use of non-steroidal anti-inflammatory drugs with a stepped-care approach and to compare the risk of cardiovascular events between patients treated with guideline adherence and those without.

Result: Between 2008 and 2011, 1,681 patients had a first-time myocardial infarction and of this, 1,076 patients used analgesics (acetaminophen and/or narcotics, or non-steroidal anti-inflammatory drugs) for musculoskeletal discomforts. Only 20% of these patients were treated non-steroidal anti-inflammatory drugs (NSAIDs) with adherence to the guideline-recommended stepped-care approach.

For analysis, guideline-concordant patients and discordant patients were propensity score matched using covariates such as age, sex, comorbidities and concurrent medications. Finally, 216 patients were included in each group.

All patients were followed until either a cardiovascular event (death, MI, stroke, transient ischemic attack, embolism) whichever occurred first or up to 2 years. In the concordant group, the number of CV events was 127 and the discordant group was 142 (p=0.137).

Using Kaplan-Meier methods, showed statistical significance between two groups (p=0.02).

Multivariate Cox regression analysis of the concordant groups showed that an increased risk of cardiovascular event exists when treated with acetaminophen and/or narcotics (HR, Hazard Ratio, 1.15 [95% CI, Confidence Interval, 0.55-2.40]), non-selective NSAIDs (HR,1.59 [95% CI, 0.73-3.47]) and selective NSAIDs (HR,4.32 [95% CI, 0.54-34.35]) compared to no medication. In discordant group, an increased risk was also found with acetaminophen and/or narcotics (HR, 1.18 [95% CI, 0.59-2.35]), non-selective NSAIDs (HR, 2.45 [95% CI, 1.51-3.98]) and selective NSAIDs (HR, 3.54 [95% CI, 1.03-12.24]) compared with no medication.

When the concordant group and the discordant group were compared, the discordant group was associated with an increased risk with acetaminophen and/or narcotics (HR,1.26 [95% CI, 0.97-1.62]), non-selective NSAIDs (HR,2.36 [95% CI, 1.75-3.18]), selective NSAIDs (HR,3.02 [95% CI, 2.29-3.99]) compared to the concordant group.

Conclusion: In this study, we analyzed the adherence to the stepped-care approach recommendations of the 2007 American Heart Association guideline when using NSAIDs in first-time myocardial infarction patients.

Also, we compare the risk of cardiovascular event between guideline-concordant group and discordant group using a national health insurance sharing service cohort database in the Republic of Korea.

Of first-time myocardial infarction patients with diagnosis of musculoskeletal discomforts, only 20% had received analgesic drugs with guideline-adherence. We found that the guideline-concordant group represents better prognosis compared to the discordant group and that use of acetaminophen and/or narcotics, non-selective NSAIDs and selective NSAIDs increase cardiovascular event risk from least to most.

The number of cardiovascular events related with the use of selective NSAIDs are much fewer than the number related with the use of non-selective NSAIDs. The reason behind such phenomenon could be due to the stepped-care approach recommendation to use selective NSAIDs only when intolerable discomfort persists despite using other drugs, such as acetaminophen and/or narcotics and non-selective NSAIDs.

In conclusion, our results suggest that increased and multidisciplinary efforts are required to increase adherence to the guideline recommendations to help prevent cardiovascular events in myocardial infarction patients when using NSAIDs.

M 20

Three Decades Research Advances in Pharmaceutics and Drug Delivery Systems: A Global View of Big Data

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Keywords: Big data, development, drug delivery, pharmaceutics, research collaboration

Method: Literatures were extracted from pharmaceutics-related journals with impact factor above 1.0 in subject category of "Pharmacology & Pharmacy" via WoS from 1980 to 2014. Combined big data and visualization tools (CiteSpace et al) were used to map knowledge structure and intellectual collaborations.

Objective: (1) To provide a panorama of global pharmaceutics/drug delivery researches by big data; (2) To investigate the research advances and future trends of pharmaceutics/drug delivery field in recent three decades.

Result: Total 27 relevant journals and 111,461 publications were identified. The annual number of publication showed a steadily-rising in last three decades. Japan had the largest contribution to pharmaceutics literatures with global share of 26.1%, followed by USA (24.8%), UK (7.4%), China (6.1%) and Germany (4.1%). But there was a continuing decline trend in Japan after 1994. School of Pharmacy from University of London ranked 1st among top ten the most productive institutions. Pfizer (2nd) and GlaxoSmithKline (9th) led the field of pharmaceutics industry.

CiteSpace program was used to detect the keywords burst, in order to find out the research fronts shifting in pharmaceutics over three decades. From 1980 to 2000, the hot keywords focused on "Prodrug", "Metabolism", "Plasma". During 2000 to present, the research area, such as "Liposome", "Microcapsule", "Nanoparticle", "Gene delivery" and "Cancer" were gained the widely attentions.

3,242 publications with citation times above 100 were considered as "high-quality publications". USA ranked 1st with 1389 articles, followed by Japan, England, Germany and France. In addition, there was a great globalization landscape of pharmaceutics researches. But for "high-quality publications", the major research institutions were mainly located only in Europe, USA and Asian. The collaborations between USA and Europe were much stronger than that with Asia.

For "high-quality publications", cluster analysis was conducted to capture the evolution of research themes and emerging trends. The result showed that the main cluster changed several years shown in ascending order of occurring years: "Structure-property relationship", "MDCK", "Gene", "P-glycoprotein", "Nanoparticle-based theranostic". The largest cluster was "Gene" that indicated it shaped the foundation of current knowledge domain in pharmaceutics. "Nanoparticle-based theranostic" was the youngest cluster showed it was a most active topic in this science domain.

Conclusion

1. Japan had the largest contribution to global pharmaceutics-related literatures, but with a continuing decline trend since 1994. USA ranked first from 2002 in annual publication number and dominated high-quality publications over years. China, showing a significant increase since 2000 in amount of publications, was going to occupy the more important position in global pharmaceutics publication share.
2. The mainstream research institutions concentrated on North America, Europe and Asia. Academic institutions led pharmaceutical researches. International pharmaceutical companies also played an important role in this field. Moreover, the strength of collaborations between North America and Europe were much stronger than other cross-territory cooperation.
3. Over three decades, the research frontiers shifted from conventional dosage form researches, analysis of drug effective components ("prodrug", "metabolism", "plasma") to advanced drug delivery systems and cancer treatment ("nanoparticle", "gene delivery", "liposome" and "paclitaxel" "cancer therapy"). It was shown that nanoparticle, gene delivery and the application in the cancer treatment were main active topics currently which were also expected to continue as hot research areas over next couple of years. In addition, according to some emerging publications, in silico formulation development and personalized medicine might receive more attention in the future.

Our research provided a comprehensive and deep insight to pharmaceutics field in recent three decades from macro-perspective. Current study could also help researchers to obtain a dynamic picture of intellectual collaborations in pharmaceutics domain.

M 21

Benefit-Risk Assessment of HPV Vaccination Program in Japan

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Keywords: Benefit-risk assessment, human papillomavirus, Japanese adverse drug event report database, vaccine

Method: To quantitative risk aspects, we surveyed public data and compared with routine vaccines. The Burden Index was calculated using disability-adjusted life year and compared between vaccination and non-vaccination. To assess benefit aspects, we surveyed incidence rate of cervical cancer in the US.

Objective: We evaluated quantitatively the benefit-risk of human papillomavirus (HPV) vaccine in Japan to assess suspended Japanese HPV vaccination program resulting from media's numerous reports on adverse events, which is different from other countries and criticized by WHO.

Result: In approval data package, the incidence of serious adverse events for HPV vaccine was 1.51%, whereas that of Polio vaccine and Diptheria-Pertussis-Tetanus (DPT) vaccine was 8.70% and 8.33%, respectively. In post marketing period, we visualized risk of HPV vaccine as well as other 6 routine vaccines using the risk-map with calculated frequency from Japanese Adverse Drug Event Report database adjusted by severity judged by three independent researchers. HPV vaccine has bigger risk than Influenza, Measles-Rubella, DPT and Japanese encephalitis vaccines. On the other hand, it has less risk than Tuberculosis and Polio vaccines. Estimated Burden Index (BI) in 10 to 44 years old women were 2.847 x 10-2 BI by adverse events in HPV vaccination group which was less than BI by cervical cancer in non-vaccination group (5.548 x 10-2 BI). The incidence rate of cervical cancer in specific age group has been decreasing since HPV vaccination was started in the US therefore the quantitative data for benefit of HPV vaccine has been accumulated.

Conclusion: Our results indicated that HPV vaccination has certain risks as equal as other routine vaccinations both before and after approval. Moreover BI could clearly show that the risk of HPV vaccination lowed risk of cervical cancer in non-vaccination group. Recent data of decreasing the incidence of cervical cancer showed the benefit of HPV vaccination. Thus, HPV vaccination can reduce risk and provide benefit, so it may increase the quality of life. The risk of HPV vaccination may be exaggerated in Japan, therefore the suspended decision of HPV vaccination program by Japanese MHLW might be questionable. Since suspension of HPV vaccination program in Japan in 2013, many Japanese women hesitate to receive HPV vaccine. We should choose whether to get HPV vaccination or not based on reliable information. However it is not enough quantitative data to estimate the benefit-risk balance of HPV vaccination. Further investigations, including the global assessments from various aspects, are required.

M 22

Trends in Endpoint Selection in Clinical Trials of Advanced Breast Cancer

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Keywords: Breast cancer, clinical trial, endpoint, outcome measures

Method: All phase II and III advanced breast cancer clinical trials registered in ClinicalTrials.gov registry between Oct 2000 and Sep 2012 were included (Cohort A: Oct 2000 to Sep 2007; Cohort B: Oct 2007 to Sep 2012). Primary and secondary outcome measures as well as trial characteristics were extracted.

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Objective: This study aims to evaluate endpoint selection and its shift in trends in phase II and phase III trials of advanced breast cancer treatment.

Result: Of 398 phase II and 120 phase III trials, the most frequently intended primary endpoint was progression-free survival in both phase types (phase II: 28.1%; phase III: 50.0%). For phase II trials, a shifting trend in primary outcome was observed from cohort A to cohort B: use of objective response rate, the most frequently intended primary outcome, significantly declined (cohort A: 60.6%; cohort B: 39.0%; P <.001); while use of progression-free survival significantly increased (cohort A: 17.6%; cohort B: 40.7%; P <.001). For phase III trials, PFS was the most frequently used primary outcome in both cohort groups with a statistically significant increase in frequency (cohort A: 35.9%; cohort B: 66.1%, P < .05). The proportions of trials using each outcome measure also differed by intervention types. For phase II, trials with chemotherpy-only intervention used objective response rate with a relatively higher frequency while those with targeted and/or hormone therapy intervention used progression-free survival more frequently. For phase III trials, similarly, trials with targeted and/or hormone therapy used progression-free survival more frequently.

Conclusion: Our study assessed endpoint selection in phase II and phase III clinical trials of advanced breast cancer, which was selected as one example of cancer as it affects millions of females around the world. For phase II trials, a decreasing trend for ORR and an increasing one for PFS was observed. Despite ongoing debate over the use of PFS as an endpoint in advanced breast cancer, it was also the most commonly used primary endpoint in phase III trials. To our knowledge, this is the first study to assess endpoint selection in advanced breast cancer clinical trials over a decade of time and as selection of appropriate endpoints is crucial for the success of clinical trials, changing trends should be considered when deciding upon primary and secondary outcomes measures to demonstrate drug efficacy and safety.

M 23

Global Effects of FDA Guidance Requiring Evaluation of Cardiovascular Risk in New Antidiabetic Therapies on Drug Development

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Keywords: Antidiabetic drug, drug development, global, guidance, US Food and Drug Administration

Method: Antidiabetic drugs approved during 1990-2015 are categorized into two groups depending on the year of approval, before the guidance (-2008) or after (2009-). The number of approved drugs, the total patient number participated in clinical trials, and the approval date difference were compared.

Objective: Our research objective is whether the guidance issued in the US have altered global trends of drug development. As a model case, we investigated antidiabetic drug development status to identify effects of FDA guidance for industry issued in 2008. Result: Our objective is to investigate about global effects of FDA guidance for industry issued in 2008. Because WHO has reported

that "All-America, Europe, and Japan will continue to account for 85 % of the global pharmaceuticals market into 21st century" (Pharmaceutical Industry, glossary of globalization, trade and health terms, WHO), we focused on the US and the other two regions: Japan and the Europe.

We analyzed three parameters related to drug development status as describing in Methods section. The first parameter we analyzed is the number of drugs approved because it reflects how advanced the drug development is. The numbers of drugs approved per year after the guidance in Japan, the Europe, and the US was 10.1, 3.1, and 3.3 times more than those before the guidance, respectively. The largest increase was recorded in Japan. The second parameter is the number of patients participated in clinical trials. We chose this parameter due to the paper reporting that the FDA guidance affected on this parameter in the US (Viereck C and Boudes P, Contemp Clin Trials 2011; 32(3):324-332). The patient number in clinical trials of individual drug in the US was significantly increased (p=0.03). This parameter in the Europe or Japan was not. This result shows that the size of clinical trials, defined by the total patient number in clinical trials, significantly increased only in the US. Finally, we investigated the approval date difference, the time lag of drug development between two countries. The approval date difference between Japan and the US before the guidance was 1515 days and that after the guidance was 69 days. The approval date difference was significantly reduced (p=0.04). The approval date difference between the Europe and the US before the guidance was 293 days and that after the guidance was 19 days. The reduction was also statistically significant (p=0.005). From this result, we assume that the issues of FDA guidance might have influenced that states.

Conclusion: In order to investigate global effects of guidance issued by FDA, we selected the field of antidiabetic drug development. In 2008, FDA issued a guidance for industry, namely Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. As the response to the guidance, Pharmaceutical and Medical Devices Agency (PMDA) in Japan and European Medicines Agency (EMA) in the Europe expressed their own guidelines, different from the FDA's. We interpreted the antidiabetic drug development trend before and after the FDA guidance in those regions as a global effect of the FDA guidance.

Due to the cardiovascular risk evaluation, large clinical trials became inevitable for the approval of new antidiabetic drugs in the US after the FDA guidance. Developing the antidiabetic drugs in the US is more expensive than before the guidance. When comparing the approval date difference, the time lag in Japan and the Europe from the US became significantly small. This result may suggest that pharmaceutical companies pursue simultaneous drug development globally. Particularly, Japan may be the appealing market since developing antidiabetic drugs in Japan does not require large clinical trials. This particular conclusion can be supported by the huge increase in the number of approved drugs after the guidance.

Our analysis suggested that a certain guidance issued in the US have affected on the drug development not only in the US but also in the Europe and Japan. This is example of having global effects of a guidance. This conclusion can be drawn because the US has bigger global influence than others. However, it is necessary to be aware of regulatory circumstance globally. Since disease knows no boundaries, a global perspective in drug development and regulatory science is essential.

M 24

Evaluation of the Appropriateness of Mupirocin Prescription in the Ambulatory Setting

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Keywords: Ambulatory setting, appropriateness of prescription, mupirocin, prescription patterns

Method: The 2010-2012 Health Insurance and Review and Assessment service-National Patient Sample dataset of South Korea was used to analyze mupirocin prescription patterns. The National Ambulatory Medical Care Survey dataset was used to quantify mupirocin prescription in the United States for comparison.

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Objective: The objective of this study was to investigate the prescription patterns of mupirocin, which is known to be highly correlated with antimicrobial resistance and to evaluate its appropriateness of prescription in the ambulatory setting.

Result: To assess the mupirocin prescription patterns, the number of prescriptions, the mean duration of prescribed use, the rate of prescriptions for over 10 day-duration and the rate of repeat prescription within 30 days as well as the diagnostic codes were analyzed. In the ambulatory setting, the annual prescription number for mupirocin was 4,683 (95% Confidence Interval, CI [4,661-4,703]) per 100,000 population, the mean duration of prescribed use was 1.14 days (± Standard Deviation, SD 0.001904), the rate of prescriptions for use over 10 days was 0.03% (95% CI [0.018-0.03]) and the rate of repeat prescription within 30 days was 8% (95% CI [7.92-8.18]). The most frequently used diagnostic code was "Viral wart" followed by "Corns and callosities", "Molluscum contagiosum" and "Local infection of skin and subcutanouse tissue, unspecified". Using the National Ambulatory Medical Care Survey data of the United States, annual mupirocin prescription rate was calculated to be 1,148 (95% CI [975-1,320]) per 100,000 population which is nearly a quarter of the rate in South Korea.

Conclusion: This study is first to investigate the patterns of mupirocin prescription in the ambulatory setting. Most of the duration of use prescribed was short with an average of one day and prescriptions for over 10 day use was rare. The rate of repeat prescription within 30 days, however, was almost relatively frequent which shows that further studies are required to investigate the rationale behind prescribing mupirocin again. The prescription amount of mupirocin in South Korea is four times greater than that in the United States and as mupirocin is an Over-The-Counter drug in South Korea and an Ethical drug in the United States, real amount of mupirocin usage could be much higher in South Korea. Most of the diagnostic codes for mupirocin use was related to surgical procedures which implies that mupirocin was inappropriately used to prevent infection rather than as a

treatment. Such inappropriate and excessive use of mupirocin can increase antimicrobial resistance development. Although use of mupirocin poses a high risk to the global issue of antimicrobial resistance, only a limited number of studies has been conducted in the ambulatory setting. We believe that our study findings will provide a valuable future resource for researchers in conducting further analyses and antibiotic resistance studies.

M 25

Do Clinical Trials Conducted in India Match its Health Care Needs? An Audit of Two Clinical Trials Registries

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Keywords: Clinical trials registry, disease burden, India, regulatory trials

Method: Regulatory studies registered between 2007 and 2015 were analyzed for year of registration, phase of development and disease burden in India (as assessed by therapeutic area of the trial), state where conducted (relative to its population). Data from the two registries was compared.

Objective: To assess the relevance of the clinical trials conducted in India to its healthcare needs by evaluating studies registered in the Indian Clinical Trial Registry (CTRI) and compare them to those registered in clinicaltrials.gov, USA.

Result: The CTRI had 3325 regulatory studies registered during the study period. From 27 in 2007, the number rose to a maximum of 550 in 2010. There was a fall over the next two years (363, 394), which rose again to 404 in 2015. Phase III trials were the maximum [1550], followed by Phase IV (783), Phase II (778), and Phase I (214). The year wise trend for the various phases was similar to that seen with the total. The state of Maharashtra had the highest number trials registered (1666) followed by Karnataka (1175) and Tamil Nadu (1004). Populous states like Uttar Pradesh (544) and Bihar (138) had far fewer trials. The North-Eastern states had no trials at all.
Disease burden expressed as Disability Adjusted Life Years [DALYs ('000)] was maximum for infectious/parasitic diseases (82,681.3), followed by neonatal conditions (66591.9), and nutritional deficiencies (19731.3). However, the number of trials in these areas was insignificant. Oncology accounted for high DALYs (24015) and also had the largest number of clinical trials [440 (13.23%)] in any therapeutic area. This was reflected in the Phase wise distribution as well with most Phase II (126) and Phase III (227) trials being in oncology. Phase III trials were also conducted in other areas that contributed to high DALYs like diabetes mellitus (148 trials, 9795.5 DALYs), pulmonology (111 trials, 41938 DALYs), musculoskeletal disorders (93 trials, 10368.4 DALYs) and digestive diseases (90 trials, 17771.3). Most Phase I trials were on vaccines (42), while most Phase IV trials were in diabetes (61).

A total of 1875 trials were registered from India in clinicaltrials.gov with the number being 230 in 2007. This number steadily rose to a maximum of 296 in 2010 after which the numbers fell only 90 in 2015. Most of the trials were Phase III (862) followed by Phase II (449), Phase I (325) and Phase IV (239). This trend was comparable in both registries. The trend was also comparable for the therapeutic areas in both registries.

Conclusion: India became an attractive destination for clinical trials after regulatory changes, which allowed conduct of global clinical trials conduct in 2005. The availability of a treatment naïve patient pool, large disease burden, experienced and English speaking investigators and relatively low costs led to further growth of this industry. Trials in both registries reflected this with increasing numbers. The fall after 2010 is likely due to the global financial crisis that occurred around 2008. New regulations introduced in 2013 hit the industry hard and this is reflected in clinicaltrials.gov registering the least number of trials in 2015. CTRI on the other hand has shown a steady upswing in numbers since 2014, suggesting that India specific trials (which may not be registered in the USA portal) may have increased. The large number of Phase III trials is a reflection of India's participation in global trials on drugs primarily discovered outside this country. The small number of Phase I trials is also unfortunate – indicating that not enough original research is occurring in India. New drug development in areas of the country's health needs is essential. Our results also show that India is not conducting trials in consonance with its health care needs, such as in infectious and parasitic diseases. It is on the other hand encouraging that a large number of Phase I studies are being conducted on vaccines which would help reducing the burden of infectious disease.

We also found a skew in the distribution of trials in the country suggesting that more efforts are needed to spread clinical trials and increase capacity across the country, so as to ensure that there is a more equitable selection of participants and better access to research. We can conclude that India must participate in more clinical trials especially in areas relevant to its disease burden. Policies to encourage new drug development in the areas where it is most needed must be introduced by the government.

M 26

Do Drugs Interact Together in Cardiovascular Prevention? A Meta-Analysis of Powerful Randomized Controlled Trials

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Keywords: Cardiovascular prevention, interaction, meta-analysis, powerful randomized controlled trials

Method: We analyzed powerful randomized controlled trials (>1000 patients) and explored heterogeneity between co-prescribed drugs and diabetes/hypertension to measure interaction (significant if $p>0.10$ and $I^2>50\%$). We illustrated the extent to which potentially significant interaction could be eliminated.

Objective: Preventive cardiovascular drugs (antihypertensive, antiplatelet, lipid lowering and antidiabetic agents) are frequently co-prescribed to treat patients. Whether these treatments interact together has never been evaluated. We explored here their interactions in terms of cardiovascular risk reduction.

Result: We explored the changes of drug effects of the four classes (anti-aggregant platelet agents-APA, antihypertensive agents-AHA, oral antidiabetic agents- ODA and statin), according to cross-exposure between them and with the hypertension and diabetes status. Comparisons of major coronary events and major vascular events between sub-group treatments were expressed by the pooled Relative Risk (RR) with 95% Confidence Intervals (CI).

In total, 19 RCTs were selected in our meta-analysis, which enrolled a total of 210 865 patients (106 563 for treatment/intensive

treatment arm and 104 302 for placebo/standard treatment arm). The follow-up durations ranged between 2.1-10 years. The quality of the studies included was relatively high: 100% low risk for selection, performance and attrition biases, 90% low risk for detection bias, >85% low risk for reporting bias and about 80% for other bias. Eight trials assessed the effect of statin (n= 58100 patients), two with APA (n= 58 666 patients), five with AHA (n = 40 329 patients) and five with ODA (n= 53 770 patients) versus placebo, except two trials which compared the effect of the same treatments but of different intensifications. Thirteen trials allowed examining the interactions between drugs used and hypertension and 10 trials allowed examining the interactions between drugs and diabetes status

The relative risks associated with these treatments ranged from 0.71 [0.58, 0.88] to 0.96 [0.90, 1.02] with statistical significances. No any significant interaction between co-prescribed medications or between prescribed medication and diabetes and hypertension status was observed in our study (p= 0.79, I^2= 0%). The lack of significant interaction did not eliminate all the possibilities of such treatment combinations. However, our results allowed eliminating treatment changes above 50% of the relative benefit for all interactions, and above 20% for the benefit of statin in hypertension.

Conclusion: Our study is the first one exploring the interaction between preventive cardiovascular drugs and with risk factors (hypertension/diabetes) in primary and secondary cardiovascular prevention, using data from the most powerful randomized controlled trials. This meta-analysis demonstrates that combining antihypertensive drugs, antiplatelet agents, statin and antidiabetics agents could be effective and safe for major vascular and coronary prevention in high risk patients. It also demonstrated that there were no interactions observed between the co-prescribed drugs and between these medications and diabetes/hypertensions status.

M 27

Evaluation of Public Awareness and Impact of the Turkish Regulatory and Reimbursement Processes on Patients' Access to Medicines

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Keywords: Patients' access to medicines, Regulatory review process, reimbursement

Method: This study included designing a comprehensive paper-based questionnaire piloted and then distributed through associations, pharmacies and clinics to 350 outpatients receiving chronic disease treatment mainly in cardiovascular and diabetes. Face to face interviews were conducted with 22 patients.

Objective: The objective of this study is to identify the public awareness and knowledge about the regulatory environment in Turkey with respect to patients' access to medicines and to evaluate the impact of the current regulatory and reimbursement process on patients' access to innovative medicines.

Result: Two hundred and ten patients (60%) completed the questionnaire (50% males). Most patients (84%) knew that medicines had to be approved by the government. Yet, 81% of patients were not aware of the regulatory review process with 73% unaware of approval timelines. Furthermore, 37% described the Turkish approval process to be of a lower standard compared to US and EU. However, 70% of patients believed that there are novel alternative medicines for their disease available in other developed countries. Similarly, 60% of patients thought that new medicines only become available in Turkey after the developed countries.

In contrast, responses demonstrated that patients know more about the reimbursement system in Turkey where the majority expressed their satisfaction and 34% described access to new medicines to be adequate. Additionally the majority of patients (75%) recognised that the government is the main payer, even though insufficient information is provided about new medicines.

Patients stated that they do not have any role in the decision-making process for approving or reimbursing new medicines and therefore most of them indicated that they need to be more involved in reimbursement (60%) as well as in the approval process (58%).

This study identified that patients on chronic disease treatment attempt to learn about their medicines and 70% believe they get sufficient useful information from various sources about their medicines' benefits and harms. Additionally patients recognise the importance of treatment compliance (85%) and are keen to report adverse drug reactions directly to their physician (91%). Therefore, it is suggested to encourage a culture among physicians to enhance the reporting of adverse drug reactions to the Turkish Pharmacovigilance Centre which is the related unit at the Turkish Medicine and Medical Device Agency (TITCK).

Conclusion: This study has demonstrated the importance of the patients' awareness, knowledge and role with regards to the regulatory review and reimbursement procedures in Turkey. When patients were asked to describe the three most important improvements in obtaining the medicines they need, they indicated access to medicines, improved health and pharmaceutical care as well as price were considered the priorities. This was despite the major challenges they perceived facing the government namely; the cost of innovative medicines is still too high as well as lack of government resources and scientific expertise.

Patients were willing to offer four principle solutions to address these concerns such as:

1. There should be more collaboration between the academic experts and government to enhance pharmaceutical policies and shorten the registration process
2. Encourage involvement through patients' questionnaires and online forms
3. The government has been successful to transform the primary health care services, therefore a similar effort must be carried out to enhance patients' timely access to medicines with lower costs
4. Doctors and pharmacists must contribute to raise the awareness of patients regarding access to medicines

The role of patients in the decision-making process of approving and reimbursing new medicines by the government should be encouraged. Patients suggested that to ensure that their needs are met in a timely way that patients' associations become more involved in decision-making and ensuring that there is a fair representation in the process. It is concluded that the use of patient questionnaires online or via doctors and pharmacists together with the use of social media could raise the awareness of patients to regulatory changes and access procedures.

T 01

Cost Effectiveness Analysis of HLA-B5801 Genotyping in the Treatment of Gout Patients with Chronic Renal Insufficiency

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Keywords: Allopurinol-induced severe cutaneous adverse reactions, cost-effectiveness, HLA-B5801 genotyping

Method: A decision model was employed to compare the cost and outcomes of treatment using HLA-B5801 genotyping with that of a conventional strategy in gout patients with CKD. The costs were obtained from SCAR patients. Outcomes were measured as an expected cost and an incremental cost-effectiveness ratio.

Objective: 1. HLA–B5801 genotyping is cost-effective in allopurinol in gout patients with chronic renal insufficiency in Korea; 2. Clinicians treating Korean patients with gout and renal insufficiency should consider HLA–B5801 genotyping to reduce allopurinol-induced severe cutaneous adverse reactions.

Result: In the base scenario, treatment informed by HLA–B5801 genotyping cost 154,000 Korean won ($138) less than conventional treatment and was associated with a greater probability of continued gout treatment without SCARs. The total expected costs of conventional treatment and treatment following HLA–B5801 genotyping were 1,332,000 Korean won ($1,193) and 1,178,000 Korean won ($1,055), respectively. The probability of SCARs during conventional treatment was 2.19%, whereas no SCARs occurred in patients whose treatment was informed by HLA–B5801 genotyping. Consequently, the probabilities of continued gout treatment without SCARs in patients treated uniformly with allopurinol and those treated based on HLA–B5801 genotyping results were 97.81% and 100%, respectively. Furthermore, patients with a probable death rate of 0.59% in the conventional method survived without SCARs following the genotyping treatment. Therefore, treatment informed by HLA–B5801 genotyping was superior to conventional treatment, considering it was less costly and more effective. Until the prevalence of HLA–B5801 decreased to 3.81%, the genotype-based treatment was more cost beneficial than conventional treatment.

Conclusion: We conducted the first investigation of the cost-effectiveness of urate-lowering treatment with allopurinol based on HLA–B5801 genotyping in Korean gout patients with chronic renal insufficiency. Our model suggests that gout treatment informed by HLA-B5801 genotyping is less costly and more effective than treatment without genotyping, and HLA-B5801 genotyping could considerably reduce the occurrence of allopurinol-induced SCARs and related deaths. The results of our study provide important information that should help prevent unnecessary adverse reactions and SCARs-related deaths and inform the development of guidelines for clinical practice and health care policy.

T 02

Practical Aspects of Developing, Implementing and Using Facilitated Regulatory Pathways (FRPs) in the Emerging Markets

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Keywords: Accelerated approvals, emerging markets, expedited pathways, facilitated regulatory pathways

Method: We identified NRAs with FRPs through Cortellis Regulatory Intelligence and web sites and developed 27 FRP characteristics. The respective NRA or a local specialist reviewed author interpretations. Characteristics were procedural or substantive and based on five sequential regulatory activities.

Objective: To assess the characteristics and common elements of currently implemented expedited (facilitated) regulatory pathways (FRPs) in use by national regulatory authorities (NRAs) in emerging economies to accelerate access to important new medicines.

Result: We assessed 33 FRPs from 29 countries. The regions with the most addressed characteristics (median number), were Middle East/North Africa (17) and Eastern Europe (17). Sub-Saharan African FRPs had the fewest characteristics addressed by their FRP (9). Consistent with the predominance of procedural characteristics in our categorisation scheme, all FRPs addressed at least twice as many procedural than substantive characteristics. The most commonly addressed procedural characteristics were having a standard operating procedure (SOP) or guidance for submitting the dossier and an SOP on how the dossier will be reviewed. The most commonly addressed substantive characteristic was whether the product must be used to treat a serious condition or where there is an unmet medical need. Of the 15 common characteristics, 11 were procedural and 4 substantive. A majority of FRPs provided opportunities for frequent interactions between the sponsor and agency's review team. Of the 24 FRPs for which a review target time was defined, all but one had a target of 180 days or less and 54% had a target of 90 days or less. Post-approval commitment requirements in the form of post-authorization studies (78%) and risk management plans (67%) were often required.

Conclusion: Emerging economies are developing country-specific FRPs to accelerate approval of medicines for serious and unmet medical conditions. This poster presents recent analyses of the characteristics, diversity and best practices observed with 33 FRPs from 29 countries and how they can be optimally used to further engagement with emerging NRAs regarding their design and implementation. This study is a first step in describing common characteristics of FRPs from emerging NRAs. We observed diversity in regional FRP characteristics, suggesting a role for further engagement with emerging NRAs regarding the design and implementation of their FRPs. FRPs will have a meaningful role in accelerating access to important new medicines. Sponsors of marketing applications for products that may fulfil unmet, serious public health challenges should seek to interact early with the NRA to determine the current state of this dynamic field, and address the current requirements based on agency feedback. Based on these results and with further research and experience, we would hope to suggest FRP characteristics that could be successfully implemented by emerging NRAs.

T 03

Sponsor Attitudes and Behaviors on Patient Recruitment: Insights from Line Management Clinical Operations Personnel

Dan McDonald
Imperial

Keywords: Clinical operations, clinical trial agreements, decision-making, enrollment, patient recruitment, site feasibility, site selection, sponsors, study feasibility, study-conduct, trial management, trial planning

Method: The method used was a survey. We sent out links to the appropriate sponsor personnel and also used 3rd party media to publish/distribute the survey. Included personnel were sponsor employees working as managers or directors of clinical operations, project managers, lead/senior CRAs, and patient recruitment specialists.

Authors: Melynda Geurts, Dan McDonald

Objective: Understand the current behaviors of clinical operations personnel at sponsor companies as it relates to patient recruitment; Identify decision-making and accountability roles with regards to patient recruitment at sponsor companies; Compare sponsor company attitudes and behaviors to industry perception, as well as the behaviors of other clinical trial stakeholders (sites, CROs, etc.).

Result: On average, 50% of the trials managed by those surveyed were delayed due to slow enrollment. Interestingly, however, half of those surveyed felt that a reasonable additional per-patient cost for recruitment on their most pivotal trials was $500 or less. The majority also felt that a site's lack of enrollment post-initiation was not unacceptable unless 90 days or more had passed. Nearly 90% of those surveyed said they selected "backup" sites but only 14% develop conditional contracts. The survey found that sponsors expect the sites or CROs to enroll patients as the majority of sponsors do not develop formal recruitment plans. In addition, over 50% of sponsor personnel rated their level of pressure or stress related to patient recruitment as very stressful. Most sponsor personnel feel empowered to make changes to boost enrollment and say that their firms are increasingly conducting trials internationally in order to help drive enrollment. The overwhelming majority feel patient recruitment is not getting any easier and just over half feel it is getting harder. Another issue they cited was that most trials have up to 3 protocol changes that impact enrollment. Only half of those surveyed said that they actually measure the impact of recruitment campaigns.

When it comes to disruptive innovations that will help to drive down enrollment timelines, the majority felt that mobile/wearables, non-site trials, and in-home study visits would be the top causes.

Conclusion: In summary, patient recruitment and enrollment continues to be one of the key contributors to why clinical trials do not complete on time. Furthermore, the majority of the respondents indicated that they still rely on the sites to enroll. And while amending the protocol and expanding sites globally are ways intended to accelerate enrollment they do not come without delays and heavy costs. The competitive landscape within clinical research is growing exponentially. Solely relying on sites to meet enrollment goals is a flawed approach. Very few studies and sites have the ability to achieve successful enrollment without some level of outside support. Sponsors will need to re-evaluate their approach to clinical trial design and planning.

T 04

Missing ePRO Data: Impacts on Clinical Trial Results

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Keywords: Clinical trial results, ePRO, missing data

Method: Literature review was conducted on the analysis and interpretation of PRO measure results. Also, data from a global web-based survey (2013) on patients who participated in at least 1 clinical trial requiring PRO entry recording was analyzed for non-compliance and patient reasons for non-compliance.

Objective: This poster will first review and evaluate the impacts of risks associated with missing PRO data to clinical trials, and then will identify and assess mitigation strategies to prevent missing data.

Result: Results of the literature review indicate that data quality and completeness is important to clinical trial results, in particular when it is being used to support primary and secondary endpoints. As PRO data are frequently used to support primary and secondary trial endpoints, the impacts of missing PRO data on trials may be significant.

Overall project risk is low when compliance rates are high (e.g., 90-100%). As compliance rates drop to <80%, the bias introduced in the results increases, the quality of the data decreases, and the risks for the data not being able to be used in the analysis rises.

The types of PRO data collected may include study medication usage for study drug reconciliation reasons, symptom presence or severity to determine eligibility for trial participation, and responses over time to indicate improvement or worsening of the symptom/disease.

395 patients provided responses on compliance in their most recent clinical trial in the survey. 53.6% (N=210) reported always being compliant with completing patient diaries; 46.4% (N=185) reported that they were not always compliant. Patients in this survey reported a high level of non-compliance for patient diaries for their most recent clinical trial, which would have a high – moderate impact on the analyzability of the data. The patients who reported they were not always compliant (N=185) provided reasons for non-compliance with their diaries which include: they forgot, are too busy, are not able to access their diary, are too sick, or for other reasons.

Each of these reasons were assessed for cause/risk, underlying issue and proactive mitigation options. For "they forgot", a cause could include that the diary schedule is confusing, and a mitigation plan could include providing alerts to sites and reminders to patients. For "too busy", the cause could be that patient burden is too high for that study, and a migration plan could include reducing the difficulty of the assessments included.

Conclusion: Although the reasons why patients are non-compliant can vary, it is important to assess the cause and risk of the non-compliance for each non-compliance reason. Underlying issues can be determined and proactive mitigation plans put in place in an attempt to optimize ePRO compliance on projects. As not all projects are the same - patient burden levels, therapeutic areas, and populations can vary largely - one must look at all of the project specifics / characteristics in order to determine a

customized plan for success. This plan, along with an understanding of impacts of missing PRO responses, is important to minimizing the time and cost associated with running each clinical trial with ePRO assessments.

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T 05

Compare the Quality of Case Reports Originating from Social Media with Spontaneous Case Reports by Evaluating Case Attributes

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Keywords: Case quality comparison, social media

Method: Case quality will be assessed using vigiGrade algorithm (Bergvall et al., 2013); a score of >0.8 represents a well-documented case. For individual case attributes, reporting fractions will be calculated. The statistical software, SAS® JMP®, will be used to prepare the statistical outputs.

Objective: The objective of this study is to compare the quality and information content of adverse event (AE) cases from a social media source (i.e., non-Company sponsored websites) with cases from spontaneous AE reporting.

Result: In this study, four Company products with social listening programs on non-Company sponsored websites were selected. The Company's Global Safety Database was searched for cases from those four social media programs and cases from all spontaneous sources; both valid and invalid cases, and only the initial version of cases were included. Cases were restricted to those received in the United States between January 1, 2011 and July 30, 2015. The primary endpoint is to compare the case quality between social media and spontaneous cases by evaluating the absence or presence of case attributes. The case attributes evaluated in this study include time-to-onset, indication, outcome, sex, age, dose, country, primary reporter, report type, and comments. Secondary endpoints are comparison of type of AEs (e.g., serious and non-serious, labelled and non-labelled) reported between social media and spontaneous cases. The preliminary analysis from the search results revealed differences in completeness of case attributes between social media and spontaneous cases. Many of the study attributes were less frequently reported in social media cases in comparison with spontaneous cases.

Conclusion: The preliminary results of this study revealed that many of the case attributes were less frequently reported in social media cases in comparison with spontaneous cases for the four Company products. The complete analysis will identify if there are differences in the quality of cases as per vigiGrade scoring between social media and spontaneous sources for these four selected products.

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T 07

Strong Considerations for Self-Reporting Prospective Suicidal Ideation Using the eC-SSRS

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Keywords: C-SSRS, eC-SSRS, suicide, suicide ideation

Method: A review of current global regulatory guidelines was conducted, centering on the 2012 Revised Draft of the FDA Guidance on Suicide Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.

Objective: This report examines the self-reported eC-SSRS (Columbia Suicide Severity Rating Scale) alternative for prospective suicide ideation and compares it to the rater-reported C-SSRS.

Result: Current literature reveals significant evidence of equivalence between self-reported and rater-reported suicide ideation, including preferences by youth and adult subjects. This report found significant mapping equivalence to all 11 C-CASA categories for both the self-reported eC-SSRS and the C-SSRS; and equivalence between the IVR and Tablet eC-SSRS. Literature confirms the eC-SSRS as ... 'an alternative approach to obtaining data on suicidal ideation and behavior.'

Conclusion: The self-reported eC-SSRS is equivalent and viable alternative to the rater-version of the C-SSRS. Two to four times more suicidal ideation events are reported with self-reporting vs a clinical interview, with youth more likely to endorse on a self-report than on an interview. In addition to regulatory and literature support, the self-reported eC-SSRS may provide additional conveniences to clinical sites.

T 08

Cost Drivers of a Hospital Acquired Bacterial Pneumonia and Ventilator Acquired Bacterial Pneumonia (HABP/VABP) Phase III Clinical Trials

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Keywords: Cost, HABP, hospital acquired bacterial pnemonia, VABP

Method: Tufts CSDD gathered benchmark data from proprietary and commercial databases, as well as references cited from literature and created a model calculating a fully-loaded (direct and indirect) cost profile of a typical phase three HABP/VABP clinical trial. Tufts CSDD, in collaboration with CTTI developed a comprehensive, detailed mapping of direct and indirect cost elements. Cost elements mapped include direct procedure costs, institutional review board fees, site costs by geography, screen failure costs, and other indirect project management costs. Model results were validated by industry experts and published sources.

Objective: A new study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) and the Clinical Trials Transformation Initiative at Duke University (CTTI) evaluates the direct and indirect phase III clinical trial direct and indirect costs of Hospital Acquired Bacterial Pneumonia/Ventilator Associated Bacterial Pneumonia (HABP/VABP), the drivers of these costs, and identifies opportunities to lower these costs.

Result: Tufts CSDD determined the fully-loaded cost of a HABP/VABP phase three clinical trials. Key variables affecting the cost of a typical phase three HABP/VABP trial can be stratified as being related either to study scope (e.g. number of sites in a study, the geographic location of sites) or to study process (e.g. the cost of recruitment and

screen fails). The cost of screen fails, as well as screen failure rates are the main drivers of cost for a phase III HABP/VABP trial.

Conclusion: Major opportunities to lower the high costs of HABP/VABP clinical trials — particularly new practices to lower screen failure rates — are discussed.

T 09

Albuminuria in Cardiovascular Outcome Trials: Balancing Event and Recruitment Rates

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Keywords: Albuminuria,biomarker, cardiovascular outcome trials, MACE, patient recruitment, UACR

Method: We reviewed data from several completed and ongoing cardiovascular outcome studies. Screening and Baseline UACR values were analysed and correlated with cardiovascular event rates. We also reviewed international and local guidelines for albuminuria testing checking recommended frequency and method.

Objective: Describe the rationale for use albuminuria (UACr) as a biomarker in cardiovascular outcome trials (CVOT); Identify challenges to recruitment that albuminuria and UACr cause when required in protocol inclusion criteria.

Result: The preliminary results of performed analyses suggest that addition of microalbuminuria to the inclusion criteria list in CVOTs significantly increases screen failure rate, even in subjects with diabetes or hypertension. In subjects with albuminuria, major adverse cardiovascular event rate (MACE primary study endpoints in CVOT) is higher as compared to subjects without micro- or macro-albuminuria. However, the enrichment of MACE events offered by micro- and macro-albuminuria does not appear to outweigh the negative impact on overall study duration caused by high screen failure rate related to the requirement of pre-existing microalbuminuria. Available guidelines for albuminuria testing are general and focused primarily on subjects with diabetes and hypertension, making addition of documented history of albuminuria to the eligibility criteria unnecessary and impractical.

Conclusion: With well-established predictive value of albuminuria, addition of UACR into the list of risk factors used in numerous CVOT protocols seems to be logical. However, there are several limitations of this approach. First, UACR is not routinely measured in many countries, even in diabetic subjects, so requirement of UACR testing in global trials can introduce regional challenges to patient enrolment. Additionally, there is a poor correlation between results of commonly used dipstick tests or local results obtained from the random urine samples and UACR values obtained from the central laboratories, making pre-screening of subjects very challenging. Unfortunately, attempts to mitigate this challenge by requiring standardization of urine sample collection leads to other operational challenges, which overall contributes to the high variability of screening and randomisation UACR results and higher screen failure rates.

T 10

Teething Problems of Global Harmonization with Regard to Bioequivalence Assessment: Proton Pump Inhibitors

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Keywords: Bioequivalence, International Conference on Harmonization, pharmacokinetic parameters

Method: The study was conducted at the FDA. Relevant materials were gathered by: (1) analyzing the current regulatory BE requirements for drug approval; (2) evaluating publically available BE assessment reviews for approved PPI formulations from the website: “Drugs@fda”.

Objective: To provide an overview of the regulatory framework for the US and EU with focus on PK parameters in BE studies; To demonstrate the differences in conducting regulatory/scientific review between the FDA and EMA using PPIs; To discuss the prospect of global harmonization in BE assessment.

Result: The US and EU regulatory agencies have established stringent requirements for the design, performance and evaluation of BE studies to ensure that only quality drug products reach the marketplace. The current statistical approach to BE assessment by both regulatory authorities is based on the “two one-sided test” procedure in which the 90% CI around the Geometric Mean of the test and reference values of AUC and Cmax is required to fall within 80.00-125.00% BE limits. The objective of these studies being to demonstrate equivalence in the “rate” and “extent of absorption” between formulations. The EMA guideline also allows in the case of highly variable drug products (HVDP) a widening of this 90%CI to a maximum of 69.84 – 143.19% for Cmax, but not for AUC, provided that the difference can be clinically justified in that there are no safety and/or efficacy concerns present. Additionally, in such a situation the EMA requires tor the acceptance interval to be widened that the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30. There is no corresponding mechanism for the widening in the US. All PPIs approved in the US met the 80-125% limits. The EMA, on the contrary, approved PPI formulations where the 90%CI limits for Cmax ranged from 69.87 to 186.96%. The estimated 90%CI for the AUC was within the 80—125% limits. Since approval a number of safety concerns with long-term PPI use have surfaced, ie fracture risk. It could be hypothesized that the high Cmax values demonstrated by BE studies could represent a risk that was not assessed during the development program where only short term usage was studied. Current usage patterns of PPIs demonstrate common treatment durations in terms of years rather than weeks. Future studies evaluating the possible long term safety concerns should be considered along with the impact of higher Cmax values on safety.

Conclusion: The FDA used more stringent BE PK criteria for approval of PPI formulations than the EMA. Consensus on Cmax issues has not been reached between regulatory agencies. Global harmonization could be the next step in the continuing process to improve BE guidelines to guarantee efficacious and safe drug products for consumers in all parts of the world. Disclosures: This project was supported in part by an appointment to the research participation program at the Center of Drug Evaluation and Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Food and Drug Administration.

T 11

Bridging the Gap: The Need for a Paradigm Shift in Clinical Trial Design to Ensure Continued Patient Access to Medicines

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Keywords: Access, clinical trial design, coverage, reimbursement

Method: Publically available NICE guidance documents and IQWiG press releases were screened for any oncology drug receiving negative appraisals by IQWiG or NICE from January 2012 until September 2015 and the key rationale was extracted.

Objective: This research aims to analyze key reasons for negative appraisals for oncology drugs by national payers in two major markets (NICE in England and IQWiG in Germany) to determine implications for clinical trial design, traditionally aimed to meet the demands of regulators (FDA and EMA).

Result: 11 IQWiG negative appraisal (defined as benefit assessments where no additional benefit was proven) and 13 NICE negative appraisals (defined as not recommended or only in research outcomes) were identified. The most commonly cited drivers for inadequate demonstration of cost-effectiveness and NICE negative recommendations were: lack of QoL data collection in the trial (5 citations), crossover post-progression confounding OS (3), methodology used to extrapolate OS curves (3), and lack of comparative trial versus the relevant comparator (3). The most regularly cited reasons for IQWiG deeming no proven additional benefit were: pivotal trial was not versus the appropriate comparator (4), lack of significant OS benefit (2), only single arm trials available (2), switching/crossover confounded treatment effects (2).

Conclusion: This research demonstrates that to ensure optimal patient access for putative pharmaceutical products, clinical trial programs must meet the increasing evidentiary demands of payers. Many of the key drivers for a product receiving negative appraisals by NICE and IQWiG were issues that could be addressed through clinical trial design (comparator choice, inclusion of QoL/utility measurements in the trial and post-progression crossover). Nevertheless, clinical trial programs are traditionally designed to meet the demands of regulators and these bodies have recently introduced expedited pathways (EMA adaptive pathways pilot and FDA breakthrough status) enabling access for certain drugs at earlier stages of their clinical development. This trend is in contrast to payer bodies which are increasingly demanding patient relevant comparative benefits that typically come from mature data packages to justify price premiums. Clinical development programs need to be developed to both produce early clinical data that can support expedited regulatory approval where appropriate but also are aligned to payer needs to ensure optimal pricing, reimbursement and market access.

T 12

Special Safety Considerations for Gene Therapy Products in Global Clinical Development

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Keywords: Committee for Advanced Therapies, drug safety, gene therapy, recombinant DNA Advisory Committee

Method: A review of regulatory guidance and legislation from regulatory bodies in North America, Europe, and World Health Organization were reviewed. Guidance and legislation were included from FDA, EMA, and ICH.

Objective: Transfer of recombinant DNA to patients poses specific safety challenges that must be appropriately monitored and mitigated by health authorities, ethics committees, other regulatory bodies and the sponsor. The various types of regulatory bodies, and monitoring and mitigation plans are discussed.

Result: At that national level the Committee for Advanced Therapies (CAT) is a scientific body that reviews Advanced Therapy Medicinal Products (ATMPs) in Europe. The approval of Clinical Trial Applications (CTA) for ATMPs is under the remit of European National Competent Authorities (NCA). If the gene therapy is particularly complex, the product may also be reviewed by the CAT. In the US the Recombinant DNA Advisory Committee (RAC) within the National Institutes of Health reviews gene therapy studies in addition to the FDA reviewing the protocol under the Investigational New Drug Application (IND). At the clinical site level many countries have committees that must approve the study separately from the ethics committee (e.g., Institutional Biosafety Committee in the US; environmental approvals in Netherlands and UK). To assist with the IBC and environmental approvals an Environmental Risk Assessment (ERA) document prepared by the Sponsor may be provided to the site. The risk group (RG) classification and appropriate Biosafety Level (BSL) or Containment Level (CL) in which the product should be used should be defined in the ERA document. Gene therapy trials pose specific considerations for the subject with regard to standard clinical trial procedures or documents. For example, the Informed Consent form should inform patients that they may be followed-up long after the study and that an autopsy will be requested at the time of their death. Gene therapy products pose a theoretical risk for cancer and reproduction. A well-developed safety management plan and independent data monitoring committee should be utilized. Clear pregnancy prevention and reporting and long-term follow-up (LTFU) plans should be detailed in the protocol. The type of LTFU program will depend on the type of vector used, propensity to integrate into the host genome and other factors affecting the risk for developing delayed adverse events.

Conclusion: Gene therapy, an advanced therapy medicinal products (ATMP), is part of one of the fastest growing sectors in the pharmaceutical industry offering great hope to patients. However, transfer of recombinant nucleic acid sequences to patients poses specific safety challenges that must be appropriately monitored and mitigated. Global clinical development of gene therapy products poses particular safety challenges that that must be monitored and mitigated by various stakeholders: 1) National level by Regulatory bodies and Central Ethics Committees; and (2) Site level by Institutional Review Boards, Institutional Biosafety Committees, Local Ethics Committees and other country specific environmental review committees. In the EU the CAT may or may not be involved in the assessment of the clinical study by the National Competent Authority or Central Ethics Committee (CEC). If a gene therapy product is particularly complex, the NCA or the CEC may request a review by the CAT, which may extend the review timelines. In contrast, the RAC is not an advisory board for the FDA but provides a separate, independent and more public review of the gene therapy protocol. A well-developed Environmental Risk Assessment document prepared by the Sponsor that is provided to clinical sites can help facilitate completion

of documentation for the site specific environmental approvals (e.g. IBC). Other Sponsor documentation that are critical to ensuring unique aspects of safety related to gene therapy clinical trials include the Informed Consent form, Safety Management Plan, Risk Management Plan, Pregnancy Prevention and Reporting Plan and Long-Term Follow-Up Plan. The type of safety monitoring during and after the clinical study is dependent on preclinical and clinical observations as well as theoretical risks such as reproductive and mutagenesis. Gene therapy has the potential to fill an unmet medical need in many therapeutic areas and with careful planning and execution can be safely developed.

T 13

Going Beyond Data Virtualization: Advancing Research with a Transformational Informatics Platform

Rick Hart
BioStorage Technologies

Keywords: Analytics, biological, data integration, platform, samples, tranformational, visualization

Method: The poster will highlight how a clinical and translational science institute (CTSI) in a leading medical academic research center integrated patient demographic and EHR, donor and sample data across their research enterprise in order to accelerate research and personalized medicine initiatives.

Objective: A collaborative data integration initiative with a leading academic research center to integrate biospecimen inventories with demographic, phenotypic and EHR data to improve knowledge sharing of sample assets across the enterprise and to accelerate research and translational research initiatives.

Result: The poster will show examples of the process and journey taken to achieve optimal utilization and identification of the best biological samples for future research. The project entailed the assessment and linking of several disparate departmental database systems (~20 stakeholders within the research enterprise). Deliverables for the project took approximately 10 months from initiation to providing visual insights to the enterprise. Resulting in the connection of scientific sample assets across the research enterprise, providing visibility of all sample assets/data, increased effeciencies in sample process, freezer utilization, capacity planning, business continuity and inventory consolidation. The result was better enterprise data collaboration among research groups and optimization of enterprise sample assets.

Conclusion: Gain an understanding on how this advanced technology solution supported the identification of the best biological samples for conducting future clinical and translational research. Learn how an advanced customized visualization platform was built to support researchers and internal biobank service personnel in accelerating access to and optimizing sample research assets. The benefits of this project include:

- Expanded visibility to integrated sample and research data by both internal biobank service providers and researcher via data dashboards
- Improved efficiencies in biobanking processes, freezer utilization, equipment validations, capacity planning, business continuity, and inventory consolidation
- Identified the need for a sample curator and resource manager roles to reduce research time in management of samples and provided capacity management of sample storage
- Enhanced support of biospecimen asset optimization for future medical research by enabling sample sharing with the enterprise
- Ability to recover costs, share sample assets and data with other collaborative research organizations to fund future research through the building of an improved technology interface for an eMarketplace with the tissue bank

T 14

The Conundrum of Fracture Risk in Users of Proton Pump Inhibitors: A Retrospective Analysis

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Keywords: Cumulative proportional reporting ratios (PRRs), fracture risk, proton pump inhibitor (PPI)

Method: The study was conducted at the US FDA. Relevant materials were gathered by: (1) Literature review of fracture risk encountered with PPI use; (2) Evaluation of FAERS data; (3) Computation and analysis of PRRs.

Additional Author: Edward D Bashaw, PharmD

This project was supported in part by an appointment to the research participation program at the Center of Drug Evaluation and Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Food and Drug Administration.

Objective: Provide an overview of fracture risk data associated with PPIs; Investigate the pattern of publications related to the topic; Outline future studies aimed to solve the conundrum.

Result: 40 articles were selected for being directly relevant to fracture risk in PPI users. Animal and in vitro studies started to appear in the scientific literature since 1998, human – since 2005. The number of publications varied from 1 to 9 per year, and increased over time. 24 studies evaluated the association between fracture risk and PPI intake. 22 out of 24 found a small statistically increased risk of fracture (OR, range 1-2). The increase in risk was found across different countries, study types, age groups. However, the results were inconsistent across these studies for a dose- or a duration-response, or time-to-onset of fracture. Many of the studies were population-based and of large size. However these studies were observational and prone to residual confounding. None of the studies reported on fatalities associated with fractures, none - accounted for OTC drug use for PPIs. 7 studies evaluated BMD in PPI users. 4 out of 7 showed a small decrease in BMD in PPI users compared to non-users. Animal studies indirectly supported epidemiological data. Cumulative PRRs showed a marginal drug-event association.

Plausible biologic mechanisms: (1) PPIs could affect osteoclasts by inhibiting the osteoclastic proton pump; (2) Chronic PPI exposure increase gastrin levels resulting in stimulation of osteoclasts by histamine and blockade of osteoclast H1 receptors by H1RAs which reduces bone resorption by mature osteoclasts; (3) Without an appropriate acid environment, Ca may be retained in food reducing its absorption/ leading to compensatory secondary hyperparathyroidism which may increase the rate of osteoclastic bone resorption; (4)

PPIs suppression of gastric acid secretion lowers folate/vitamin B12 absorption leading to alterations in homocysteine levels that may contribute to increased fracture risk; (5) Dizziness/confusion as side effects of PPIs may increase the likelihood of falls. Overprescribing and long term PPI use are plausable explanation.

Conclusion: The long-term safety issues such as an increased fracture risk in PPI users cannot be excluded. Overprescribing and long-term PPI use that was not considered in the original risk-benefit approval "metric" are plausible explanations, though no definite conclusion can be drawn from the studies conducted so far. Future studies evaluating the change in PPIs prescription pattern over time are needed. The ability to do these studies will be hampered by the expected exiting of the marketplace by innovator companies once marketing becomes economically less viable. In such situations, the lodging of the data in a university consortia or in a "safe harbor" may be necessary to ensure the ability of such long term evaluations to be made.

T 15
Impact of Risk Evaluation Mitigation Strategy on Use of Erythropoiesis-Stimulating Agents

Kristen Hollingsworth
Johnson & Johnson

Keywords: Food and Drug Administration (FDA), risk evaluation mitigation strategies, safety warnings

Method: Retrospective observational study utilizing Medicare 5% sample data in patients with breast and lung cancers. Observational Periods: Pre-REMS: 1Q2008 – 4Q2009; Post-REMS: 1Q2010 – 4Q2011

Objective: To determine if a significant difference exists in the proportion of Medicare patients with breast and lung cancers with CIA treated with erythropoiesis-stimulating agents (ESAs) pre and post-REMS.

Result: ESA use decreased sharply in breast and lung cancer patients and reached statistical significance in both ($p < 0.0001$); patient categories were not impacted differently.

Breast Patient Group-Pre-REMS: Sample Size: 493, ESA: 387,Use 78.5%; Post-REMS: Sample Size: 562, ESA: 295, Use 52.5%; Unadjusted OR: 0.30; 95% CI: [0.23;0.40]; p: <.0001; Adjusted OR: 0.32; 95% CI: [0.23, 0.40]; p: <.0001.

Lung Patient Group-Pre-REMS: Sample Size: 1,083, ESA: 904,Use 83.5%; Post-REMS: Sample Size: 1,198, ESA: 698, Use 58.3%; Unadjusted OR: 0.28; 95% CI: [0.23;0.34]; p: <.0001; Adjusted OR: 0.27; 95% CI: [0.22, 0.33]; p: <.0001.

Conclusion: ESA use decreased in breast and lung cancer patients and reached statistical significance in both; patient categories were not impacted differently. Decrease in ESA use post-REMS implementation was found for patients with both breast and lung cancers and was statistically significant. Patient categories were not impacted differently. These results confirm previous research of an impact of safety warnings on the use of ESAs. (Previous research focused on implications of the National Coverage Determination and black box warning on the use of ESAs.)

T 16
Best Practices for Medical Review Process in Clinical Research

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Celldex

Keywords: Clinical research, clinical trial, data cleaning process, data quality, data review, medical director, medical review, patient profile

Method: We reviewed our internal processes and external practices from publications and purposed several principles to streamline the processes for better quality and efficiency. We examed a number of studies in the past and summarize the processes and best practices.

Objective: Medical review on clinical data is a comprehensive reivew of patient data in the database. It is different to data cleaning and source verification by the data managers and site monitors. It involves the sponsor or CRO medical team. The task is critical for data quality and study timelines. However, the complexity is often under-estimated by the study team.

Result: Timing: medical review should start as early as possible when data are entered into the database for the first few patients enrolled at each site. The focus should be on eligibilities against CRF data for demographics, baseline disease characteristics, medical history and pre-trial symptoms and medications. Early identification of issues may prompt protocol modification or retraining. Later review should focus on AEs, reason for DC and study endpoint measurements. Tools: To facilitate medical review, relevant CRF data for a patient from different panels should be pooled in an easy format (patient profile) mincing patient chart in practice. Patient profiles are often developed and programed out of J-review with decoded information. A review tool with visual presentation is preferred. Data listings can be effective to target known issues identified during individual case review. However, the patient profile is essential for comprehensive medical review. It is helpful to have access to patients EHR directly by the medical team.

Communication: Issues identified during the medical review should be clarified and resolved with the investigator via data queries. The query flow can be tracked by DM. The process should ensure the query clarity for all parties (DM, Monitors and sites) involved towards query resolution without delay and re-query. For important issues, contacting the investigators (via a local medical monitor) and direct access to the source data is encouraged. For common and generalized issues, additional listings and/or edit checks can be programed for automation and re-training should be considered.

Conclusion: Medical review conducted by the medical group is essential for data quality but the process is largely driven by DM. The timing could be optimized to avoid repetition with focus on key aspects of medical quality. Effective tools such as patient profiles complimented by data listings are required for reviews. Clear communication among all parties is essential for medical query resolution. A feedback system can be built in the process to address identified issues programmatically. Optimal medical review process is needed for medical quality of the data.

T 17
Mobile CRAs: Transforming Clinical Monitoring Processes through Mobile Technology

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Keywords: Clinical operations, CRA productivity, innovation, mobile technology, process improvement, quality

Method: CRA delivery in Asia was assessed for this investigation. Four mobile applications were introduced and grouped (save time, improve quality, both) where qualitative and quantitative assessments were made before and after the introduction of these tools.

Objective: This investigation looked at comparing CRA's on-site delivery through specific mobile applications developed specially for clinical monitoring; with the main aim to access the potential productivity and quality gain as compared to the current processes.

Result: The following four mobile applications were deployed in Asia between 2015- 2016 to aid an on-site CRA:
CRAs were accessed based on the average time used in conducting a particular task using the mobile app vs conventional method. Median rate of time saved is calculated.

1. IP Calculator: Calculate patient's drug intake compliance.
   a. Productivity: 3.54H/ CRA/ year
   b. Quality: Reduce human calculation error by reducing variation of processes
2. Subject Visit Scheduler: Calculate the acceptable visit window range of a patient and keep track of patient actual visit date.
   a. Productivity: 0.97H/ CRA/ year
   b. Quality: Reduce human calculation error by reducing variation of processes, good reference for site to remind patients, reduce visit window related PDs, enables CRA to have oversight of patient visit window before going to site.
3. Mobile Camera Scanner: Provides high quality scanned documents & print outs, saves printing time when a CRAs are at site where photocopier may be located far from their work station.
   a. Productivity: 7.76H/ CRA/ year
   b. Quality: Comparable and better scanned/ print quality as compared to some photocopier and scanner.
4. Prohibited ConMed: Protocol & country specific drug directory that display information of a searched drug and if the is allowed, prohibited or restricted.
   a. Productivity: 16.88H/ CRA/ year
   b. Quality: Reduce the need of cross reference of several documents and reduce human error.

Overall results shown that mobile applications catered specifically for clinical monitoring drives improvements in terms of time save, compliance, consistency and potential reduction in quality related incidents.

Conclusion: While the clinical research industry has sometimes lagged behind others in the adoption of mobile technology, mobile diagnosis, wearable technology and patient-focused applications have all seen a number of recent advancements. Where there is still a gap is in the usage of such tools to improve the clinical development and the clinical monitoring process itself. By identifying specific key and unique activities that CRAs execute during on-site monitoring, we were able to identify and develop a number of mobile applications to improve the efficiency of the monitoring processes. Usage of these mobile tools led to significant time and cost savings, as well as improvements in quality and patient safety. One example would be the Prohibited ConMed App, which provides an automated method for assessing concomitant medications alone, was able to save approximately 17 hours of on-site time per CRA, per year. By scaling to the magnitude of CRAs across the globe, the time savings would be enormous.

With clinical research attributing approximately 70% of drug development costs, which can amount to more than $37,000 per day, there is an urgent need to address productivity in trials. Further assessment of clinical trial and monitoring processes through the lens of mobile technology will surely allow further improvements in this area – reducing costs, accelerating development time and improving the rate at which new drugs reach patients.

T 18
Comparing the Equivalence of EQ-5D-5L PROM Across Paper and Electronic Modes of Administration

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Keywords: eCOA, ePRO, ePROMs, EQ5D5L, equivalence, PRO, PROM

Method: A mobile EQ-5D-5L version was developed with guidance from EuroQol. 200 respondents from Yorks, UK were randomly allocated paper or mobile administration modes based on age, gender and self-reported health issues. Respondents were asked to complete the EQ-5D-5L and follow up usability questions.

Objective: Recognize the interest in delivering Patient Reported Outcome Measures (PROMs) using mobile devices
To demonstrate the steps required to implement an eCOA assessment for use in a clinical trial.

To describe the lessons learned from this implementation and to convey these to an audience.

Result: EQ-5D equivalence was compared at the dimension and utility and VAS score level using ANOVA. Response rates were comparable across the arms, with the majority of respondents owning a smartphone. The mean EQ-5D-5L utility and VAS scores and the frequency of respondents endorsing the individual EQ-5D-5L categories across each of the dimensions does not differ across the administration modes. The majority of the mobile phone completion sample agreed that the mobile version of EQ-5D-5L was easy to complete, and that the phone was easy to use, and that they would complete e-PROMs again.

Conclusion: Completing e-PROMs using mobile phones produces equivalent results and response rates to pencil and paper methods, and respondents are positive towards completing questionnaires using these methods. A follow up study comparing the same measure across different sized devices and operating systems is in progress.

T 19
Stack, Swarm, Arc: Data Visualizations

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Keywords: GxP, metrics, quality, visualizations

Method: Not a study but shows the use of visualizations in QA.

Objective: Data visualizations in combination with the expertise of a QA personnel such as Quality and risk identification and root-cause analysis can transform the way quality is managed.

Result: Metrics has been used in the clinical research industry for many years to measure quality performance. Despite use of such metrics occurrence and recurrence of quality issues are not uncommon. One of the key challenges is the task of aggregating and decoding large number of data points. In the context of Quality assurance, the complexity increases because of the onerous task of requiring to correlate, identify outliers, patterns to zero in on anomalies to probe into processes and root-cause analysis. Data metrics provide information to certain extent but in the practical sense it means connecting many dots to determine insights. Recent advances in technology has complemented this process well through data visualizations.

Conclusion: Transforming Quality metrics into insights and the way ahead.

T 20
US Outcomes-Based Drug Pricing: A Fad or the Future?

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PAREXEL

Keywords: Health technology assessment, market access, pay for performance, pricing, reimbursement

Method: Health technologies that have been publically reimbursed with a performance or financial based risk sharing scheme were identified from the relevant payer body website up to 7th December 2015 (UK: SMC and NICE, IT: AIFA, AU: PBAC). The date, indication and type of agreement were extracted.

Authors: Richard Macaulay and Patricia Cost, PAREXEL Access Consulting

Objective: Pay-for-performance deals have been recently agreed with major PBMs and insurers for Repatha and Entresto. This research analyses experiences in UK, Australia and Italy to inform a discussion on whether such agreements could form part of a new US drug pricing paradigm.

Result: In England and Wales, 61 indications are currently recommended by NICE with risk sharing agreements (RSAs - termed Patient Access Schemes [PAS] in UK), 42% for oncology indications. 74% of these are simple discount schemes, with 24% being more complex financial schemes (free stock, dose caps, rebates) and only 2% (n=1) being performance based. This one performance based scheme was also the oldest NICE PAS in place. Previous experience with performance-based Risk Sharing Agreements [RSAs] was identified in Multiple Sclerosis where a large cohort of patients using interferon beta were to be followed for 10 years from 2002 and price decreases triggered if outcomes were worse than predicted. However, despite negative findings from an initial readout in 2009 (outcomes were not only worse than predicted but were worse than untreated controls) price reductions were not realized due to concerns about the model, despite the significant time and resource invested in this. In Scotland, 79 SMC recommendations were identified with a PAS: 86% were simple discounts with only 1% as performance based agreements and 5% complex financial based schemes (8% other/unclear); 43% RSAs were for oncology indications. In Italy, AIFA have 79 drug indications under monitoring with RSAs in place: 64% are performance-based, 33% are financial-based, and 3% have both; 77% of RSAs were for oncology indications (57% of financial-based and 88% of performance-based RSA). In Australia, from Aug 2014 to December 2015, 28% (48/173) PBAC appraisals included a RSA, 71% (34/48) of which were recommended (compared with 61% [72/118] of those lacking a RSA). 57% of these RSAs were financial based, 6% were managed entry agreements (where a temporary price is agreed pending further evidence generation) and only 4% were performance based (33% not stated/unclear).

Conclusion: Recent performance based agreements agreed by PBMs and insurers as part of the coverage decisions of Repatha and Entrestro suggest that benchmarking prices to patient outcomes could provide a new paradigm for drug pricing in the US. Data presented here illustrate that even in single payer health systems, performance based pricing is a relative rarity outside of Italy. The typical mechanism utilized to reduce costs to payers and secure national reimbursement is a confidential discount on the list price. NICE in particular have previously agreed several outcome-based RSAs but have found these difficult and costly to administer alongside difficulties in clawing back rebates where outcomes are not realized. The US is also a much more fragmented healthcare landscape, where tracking patients and outcomes is even more challenging. Nevertheless, it is notable that Italy continues to utilize performance based RSAs for oncology therapies as part of the AIFA ONCO registry, indicating that where the infrastructure exists, these can be an effective way of ensuring value and controlling costs. Outcomes-based pricing is now also being re-introduced in new forms in other markets. In Australia, newly established managed entry schemes have enabled reimbursement for drugs based upon a temporary price to be revised based on future, potentially real world, evidence. In England, a national oncology registry (SACT) is being established which could be used as a basis for future performance-based RSAs. Indeed, the Cancer Drugs Fund has beeen recently reformed into a temporary reimbursement fund to produce real world data to help inform future NICE appraisals. In conclusion, implementing outcomes-based pricing has been widely viewed as very challenging ex-US and until the correct infrastructure has been built to adequately track patients and enforce rebates it may take many years to become widely established in the US.

T 21
Risk Assessment of Sites Through Risk-Based Monitoring (RBM): Do Your Monitors Agree? A Joint Case Study

Nick Hargaden
Algorics

Keywords: Case study, data visualization, data-driven, RBM, site monitor, statistical model

Method: This blinded study was conducted in Sep 2015 along with the monitoring and management team at Neuroscience Trials (NT), Australia. Site anonymized data was collected, data-driven, visualization enabled manual review, and risk assessment of sites was performed. This was then validated with NT monitors.

Additional Authors: Abby Abraham, Vice President, Clinical Solutions; Tina Soulis, General Manager, Neuroscience Trials; Nick Hargaden, President, US Operations

Objective: The primary objective of this case study was to understand whether a simplified RBM approach that is data-driven could provide a view of site risks and also whether such an approach is congruent to study monitor's perception of risk at sites who had used conventional on-site monitoring techniques.

Result: Data from a completed Phase 2b study involving acute ischemic strokes from 12 sites and 77 subjects was provided.

- The protocol was reviewed by Algorics team and inputs pertaining to the Protocol were received from Neuroscience trials team. Factors that can be a potential risk to conduct of the study were identified. Additional risks related to what is reviewed from site monitoring was also factored in and finalized.
- Risk scoring process: Each risk parameter is provided a graded scoring guideline which is dependent upon the degree of impact it could cause on the outcome of study conduct. The aforementioned risk parameters were mapped from the study data report and data visualizations and thresholds were built for these risk parameters so as to easily and effectively review data by Algorics team. Subsequently, two types of analysis was used.

1. Manual review of data and deriving a site risk score.
2. Data-driven model on specific parameters (Percentile and k-means cluster models) that could provide insight into certain aspects of site's functioning which could be linked to site's functioning and thereby risk profile.

- The following are the key observations upon analysis of data through both approaches:
  - Consistency of risk classification (75% incidence and above) of sites across Manual data review and the two data-driven models: 70%
  - Consistency of risk classification of sites across manual data review and at least one data driven model was 70%. (Sites C,E & J)
  - Consistency of risk classification across both data-driven models (K-means cluster and percentile method on time to groin puncture delay) was 80% (Sites A,B,C,D,E,G,H,I)
  - High risk and medium risk classified site in manual data review that coincided with one data-driven model (Percentile method on Groin puncture delay): 80% (Sites C,E,F,H & J)

This was validated with the relevant site monitors whose impression of high and medium risk sites coincided with the data-driven model.

Conclusion: This exploratory exercise helped in drawing the following conclusions:

- Manual data review when performed in an objective and risk based approach was able to detect risks at site. Application of this approach during source data review (SDR) can significantly help in continually assessing risk of sites based on monitor's feedback.
- Though there may be reservations about using data-driven models to assess risk, this case study demonstrates that when certain important processes executed at sites that are critical to study outcomes are selected and the data is run through relevant data-driven models, it does provide insight into how sites are functioning. This can be an important input to determine risk at sites proactively.
- Manual data review when complemented with simple data-driven statistical models could increase the likelihood of characterizing a site risk profile.
- In order to perform risk based approaches to monitoring, execution of such a process can be enabled through the use of clinical technology solution that helps in risk planning, data visualization and data-driven statistical modeling.

The use relative ease of use of data visualizations was demonstrated. NT team was provided access to the data visualizations system (Acuity) and they reported that a single complete subject review took about 25 mins initially for review. This subsequently reduced to about 15 mins after getting used to the tool and the modified review methodology. This proves the need of such a technology platform to increase efficiency and effectiveness of data review in conventional monitoring models as well as in RBM.

T 22
Comparative Strengths of Public and Commercial Clinical Trials Databases: A Case Study

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Keywords: Clinical trial databases, comparative case study, competitive intelligence

Method: The following clinical trial databases were searched: NIH ClinicalTrials.gov, EudraCT, ICTRP, Citeline TrialTrove, Adis Clinical Trials Insight, and Cortellis. Searches were repeated after 30 days to evaluate updates.

Objective: In this case study, commercial and public clinical trials databases were searched for a chosen disease in order to evaluate differences in trial coverage and content.

Result: The study evaluates differences in trial coverage and content between the six databases. Some trials are retrieved from all databases, others are retrieved from several databases, and some are unique to a particular database. These coverage differences are sometimes due to index terminology differences (for example, the disease may not be indexed according to the search terms), to lack of indexing for the searched disease, or the trial may not be present in the database(s). Content for the same trial will also vary between databases, due to variation in database structure, update frequency, and trials covered.

Conclusion: Each of the commercial and public clinical trials databases have different strengths in coverage and content. Some databases provide excellent information for a specific country or region, while others provide global coverage. Commercial databases tend to focus on key therapeutic areas. And each database provides different levels of indexing and vocabulary/data standardization. The case study will illustrate how elements of unique content in each database can be used to support competitive analysis and trial planning.

T 23
Patient Reported Outcomes: Comparison of Required Data Cleaning Efforts for ePRO Versus Paper

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Keywords: Data cleaning, data quality,electronic patient reported outcomes (ePRO), patient reported outcomes

Method: As PROs are used as endpoints, high quality data is critical. Data cleaning is a process that occurs prior to analysis to ensure data integrity and reliable results. This poster will describe the data cleaning process and will compare the data cleaning requirements of paper PROs to those for ePRO.

Objective: This poster will illustrate the impacts of low quality PRO data, describe the data cleaning process, compare the process for paper versus ePRO and provide

recommendations of how ePRO can be implemented to decrease the level of effort of data cleaning.

Result: Data cleaning consists of querying, diagnosis, and resolution.

The following data queries will be compared: identify records with missing or out-of-range dates / times, missing responses, missing records (entire record / entry), outliers / out-of-range values, contradictory responses / inconsistencies / strange patterns, and extraneous / excess data.

Diagnosis includes determining an error's root cause, confirming missing data, verifying corrective actions, and concluding the issue is unable to be diagnosed. For paper, cross-checking the original paper source is needed to identify if the error is associated with patient entry / staff secondary entry or if data is truly missing. For ePRO, many data cleaning steps can be reduced or eliminated. For instance, as ePRO entries are time / date stamped, data cleaning for missing dates is not needed. ePRO can include time windows to prevent out-of-range dates / times. ePRO systems can be programmed to either prevent skipping responses or to confirm if a patient intended to skip that response, therefore confirming missing responses would not be required. ePRO systems can also be designed to prevent out-of range values, thus eliminating this data cleaning diagnostic. With direct patient data entry, human error introduced with secondary data entry is eliminated. Extraneous / excess data would not exist in ePRO systems as patients would not have the ability to provide two responses when only one is required or be able to write in additional information.

Resolution involves handling identified issues: corrections and marking data for exclusion from the analysis. When the original paper is lost, data may be excluded since accuracy cannot be confirmed. Since patients directly enter their responses in the ePRO system, the ePRO data is the source data, so verification can be done directly without having to search / locate an additional source.

Conclusion: As PROs are used as study endpoints, high quality data is critical. Data cleaning is an important process that must occur prior to analysis to ensure data integrity and reliable results. Low quality data can negatively impact analysis, results, and costs. End-of-study time is precious; timely results are needed for submissions. When comparing the effort of data cleaning for paper versus ePRO, the difference is substantial. ePRO can ensure high quality data and optimize timelines by reducing data cleaning time.

Data cleaning paper PRO data can be a time consuming process, as it often is like detective work with searching for missing pages, searching to reference the original paper to decipher correct responses, etc. While implementing a high quality ePRO may take more time and money at the study's start compared to paper, ePRO can reduce time required for data cleaning with preventing errors and producing higher quality data with higher patient compliance. If ePRO systems are well-planned / implemented, a number of data cleaning processes are no longer needed.
Data cleaning process may identify a high amount of missing data. Missing data can also impact the data's analyzability, where if there is a large percentage of missing data, the impact can be significant. A number of data cleaning steps require going back to the original paper form to confirm, which can be an issue if the original paper form cannot be found or if the original paper form got corrupted, making it impossible to provide confirmation. If any findings from the queries cannot be confirmed with looking at the original paper form, this data may have to be set to missing. Well-planned ePRO systems can produce higher quality data and also higher patient compliance, so the amount of missing data is substantially reduced. When implementing ePRO, proper planning should be done to benefit from the advantages of ePRO.

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T 24

Patient Recruitment on Social Media: a Qualitative Analysis of Strategies by Pharmaceutical Companies on Facebook and Twitter

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Keywords: Good clinical practice, patient engagement, patient recruitment, social media

Method: A retrospective, qualitative analysis was performed examining posts from pharmaceutical companies on Facebook and Twitter aimed at recruiting subjects for clinical research. Screenshots of posts are displayed and analyzed in context of ICH Good Clinical Practice (GCP) and FDA social media guidance.

Objective: The objectives of the study are to analyze different usage strategies of social media in clinical trial patient recruitment by pharmaceutical companies and contract research organizations, and to examine each strategy from an ethical and regulatory viewpoint.

Result: Five examples of varying methods and demographics are characterized and evaluated in the study. 1) A large EU-based pharmaceutical company aggressively uses Twitter and Facebook to recruit US patients and healthcare professionals for specific oncology clinical trials, including a separate Facebook account solely dedicated to oncology clinical trial recruitment. 2) A small Canadian biotechnology company promotes a specific trial to irritable bowel disease (IDB) patients on Twitter, including a phone number, email address, and website for interested patients. 3) A large US-based contract research organization (CRO) uses Facebook to enlist healthy volunteers for early phase research, including specific payment amounts in their posts and utilizing a 'Sign Up' button at the top of the page. 4) A large US-based pharmaceutical company launches a Twitter dedicated to clinical trials, but uses it only to educate patients on the fundamentals of clinical research without links to actual studies. 5) A large US-based biotechnology company uses promoted (sponsored) Twitter ads to recruit ulcerative colitis patients.

Conclusion: Over 50% of pharmaceutical companies have a footprint on social media but these companies engage in very different breadth of activities on these sites. Only a minority of companies (<5%) use these platforms to recruit patients or researchers for clinical trials, and within that minority, the strategies differ greatly. Some companies' approaches are very conservative, educating readers about clinical research or celebrating patients that have advanced science by participating in clinical trials, while other companies' approaches more closely straddle ethical and good clinical practice boundaries by potentially unduly influencing patients with compensation figures or not mentioning other treatment options. As more and more companies engage with patients on social media and as clinical trial enrollment

is becoming increasingly competitive in several disease states, it will be important for companies to utilize social media for trial recruitment and this analysis will show them various methods that have been used in context with this industry's regulated environment.

T 25

Cultural Adaptation of the TOMMORROW Cognitive Battery in Russia, Switzerland, and Italy

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Keywords: AD, cognitive assessment, cultural adaptation, MCI, translation

Method: Linguistic and cultural adaptation of the cognitive battery was completed in Russia, Switzerland (German), and Italy. Professional translation was followed by in-country cognitive debriefing. In-country psychologists provided input on construct validity and appropriateness for the target population.

Objective: To describe methods and results from a comprehensive linguistic and cultural adaptation of the TOMMORROW cognitive battery, designed to detect transition from normal aging to mild cognitive impairment due to Alzheimer's disease (MCI-AD) in multi-national clinical trials.

Result: Final recommendations for revisions to translated tests were based on feedback from in-house psychologists, expert reviewers, testers, and subjects engaged in cognitive debriefing. In all countries, alternative wording was recommended to clarify task demands and increase understanding by the target population. Significant adaptations to the Multilingual Naming Test (MINT) were requested. Regional responses were incorporated and improved pictures were provided. The picture of one naming item, the "plug," was adapted for each region.

For Russian measures, changes to initial translations were made to achieve cultural equivalency of task instructions. In addition, Russian feedback indicated potential differences in speed of processing tasks due to a cultural emphasis on accuracy, reduced exposure to alphabetical sequencing (TMT-B), and relative unfamiliarity with timed testing.

A significant change to the Italian MMSE included revision of the "No ifs, ands, or buts" equivalent to improve construct equivalency and maintain consistency with common practice. Additional changes included revision of the TMT-B to remove letters J and K, and substitution of letters for the lexical fluency task.

Regarding the German language, Swiss reviewers expressed a preference for Swiss German over High German words. To facilitate more widespread use of the final adapted measure, the decision was made to adhere to High German vocabulary. Suggestions regarding revisions of CVLT-II categories were beyond the scope of the present project. As such, recommendations for improved translation of items were incorporated, but alternate words and word lists were not. Although cultural differences in CVLT-II category frequency have the potential to influence raw scores, collection of region-specific normative data completed following cultural adaption can mitigate the impact of these differences by allowing for normalization of raw scores relative to a culturally appropriate standard.

Conclusion: Cultural adaptation of cognitive assessments improves the quality of translated instruments by ensuring tasks, stimuli, and instructions are understood and are appropriate for use in populations of interest. Successful adaptation for clinical trials ensures cultural appropriateness of performance-based tests while maintaining the construct validity and integrity of the original instruments.

Linguistic and cultural adaptation activities contributed to the development of improved, culturally appropriate versions of the TOMMORROW cognitive battery for use in German, Russian, and Italian. Results suggest proposed methods for cultural adaptation of performance-based assessments can identify and correct errors prior to use in clinical trials, yielding potentially widespread gains in the reliability and validity of translated instruments.

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T 26

The Impact of Regulatory Policy on the Development of Clinical Trials in Taiwan

Jessica Chou
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Keywords: Clinical trial, project management, regulation, Taiwan

Method: From 2009 to 2015, the database of reviewing investigational new drug applications in Taiwan was assessed to identify indicators of regulatory performance measurement. Also, the information of trials and sites for the treatment of major diseases in Taiwan was compared with other countries.

Objective: In order to protect patients and improve clinical trials, specific regulatory policies for clinical trial environment have been developing in Taiwan. This study is to review these indicators of the evolution of the clinical trial regulation and analyze their impact on clinical trial competitiveness.

Result: The number of clinical trials in Taiwan has significant increase correlated with implementing new regulations and strategies through efforts of government, industry and academia. Particularly, the phase I and Phase III studies are growing greatly. 85% of the studies were sponsored by foreign companies. And, 70% were multiregional clinical trials. The major hospitals involved in clinical trials were given AAHRPP accreditation, IRB/c-IRB function and brought significantly more clinical trials to support new drug premarket approvals.

Recently, fostering competitiveness of clinical research in Taiwan, such as speed of approval, patient recruitment, personnel experience and training, visibility of centers of excellence, has emerged.

Conclusion: Clinical trials offer critical path to discover new or promising therapies. The regulatory environment for clinical trials is considered to affect a company's decision on multi-regional clinical trials. This study is intended to recognize clinical trial competitiveness in Taiwan induced by the evolution for the international harmonization of the GCP in Taiwan and strategies for streamlining clinical trial regulation. This study establishes the current regulatory performance and their impact on boosting clinical trials in Taiwan. The critical successful factors on fostering competitiveness of clinical trials require sustained monitoring and measurement.

T 27

So You Want to Influence Stakeholders... Now What? How Outreach Programs can Advance Clinical Research

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Keywords: Clinical trials, project management, public health, stakeholder communication

Method: An outreach program involving 1) face-to-face interactions, 2) in-person, webinar-based, and on-demand trainings, and 3) development and deployment of tools and resources was implemented to ensure regulatory and procedural compliance and the successful conduct of complex HIV/AIDS clinical trials.

Objective: To share how a US Government Agency, sponsoring a global portfolio of HIV/AIDS clinical trials, leveraged a CRO relationship to optimize communication strategies and knowledge sharing with stakeholders via an outreach program promoting regulatory compliance and successful clinical trial conduct.

Result: Engagement with external stakeholders and the use of metrics to identify issues and document issue resolution have been critical to the success of the multipronged outreach program created and advanced by a Government-CRO relationship. The Division of AIDS' Regulatory Support Center (DAIDS RSC), which is run by the CRO, has been integral to the proactive identification and resolution of stakeholder issues. Stakeholder engagement via face-to-face outreach such as Information Booths and consultative sessions held by the DAIDS RSC at network meetings, presentations and meetings with DAIDS' clinical trial Network Operations Centers, as well as a "DROP-IN" program where DAIDS and DAIDS RSC personnel meet clinical trial site staff on location, have been used. Electronic engagement methods such as tutorials and e-Learning, as well as tools and resources such as checklists, and how-to videos, made available via the public and mobile-accessible website, created and maintained by the DAIDS RSC, have also been used for certain tasks. Project management principles have been applied to these outreach efforts, such as: 1) the systemic roll out of e-Learning modules to optimize the use of new DAIDS policy manuals on safety reporting and essential document submissions; 2) the delivery of training to remote international locations in planning for audits; and 3) the implementation of applicable procedures to ensure cost-effective compliance with regulations during the protocol lifecycle. These outreach efforts have helped the Government to proactively identify and address gaps in awareness about available clinical research resources, process inefficiencies, and other issues, such as optimization of the use of a Clinical Trial Management System (CTMS) called the NIAID Clinical Research Management System (N-CRMS), as the database of record for DAIDS' large global clinical trial portfolio.

Conclusion: The Government–CRO relationship has been an integral part of the Government's efforts to implement more efficient processes and maximize the use of new technologies to advance HIV/AIDS clinical research (including >230 active protocols under ~90 INDs) being performed by >360 DAIDS clinical research sites in >20 countries around the world. The face-to-face and electronic stakeholder engagement methods, as well as the resources and tools made available on the DAIDS RSC's public, mobile-accessible website through the outreach program have all led to effective sponsor oversight and improved efficiencies that have helped to optimize clinical research operations across DAIDS, the DAIDS RSC and DAIDS' other stakeholders. In addition, the project management principles applied to the coordinated, systematic roll-out of various parts of the program, such as e-Learning modules developed to coincide with the launch of new DAIDS policies, as well as continuous analysis of the impact of these programs, have been crucial to the success of the outreach efforts. The stakeholder engagement experience with the DAIDS RSC shows that the Government can effectively leverage its CRO relationships to develop and implement an outreach program to facilitate the support of critical clinical research in advancing the fight against HIV/AIDS in diverse regions around the world, including clinical trial sites in resource-limited settings. (This was supported by DAIDS, NIAID NIH contract HHSN272201000013C.)

T 28

Maximizing Awareness of Post-PharmD Opportunities in Industry Through Targeted National and Regional Recruitment Initiatives

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Keywords: Biotechnology, fellowship, industry, PharmD, recruitment

Method: Recruitment events included career fairs, regional/national conferences, pharmacy school visits, and virtual sessions. Surveys were collected from student attendees to gather metrics on academic affiliation, anticipated year of graduation, and how they learned about the program.

Objective: The MCPHS University Biopharmaceutical Industry Fellowship Program attended recruitment events in 2014 and 2015 to increase knowledge and awareness of postgraduate training opportunities among PharmD students. The objective is to assess the reach of these events to enhance future recruitment strategies.

Result: In 2014, the fellowship program attended 36 recruitment events (in-person: 27 | virtual: 9) across 20 different states. In 2015, the fellowship program attended 43 recruitment events (in-person: 39 | virtual: 4) across 25 different states. In 2014 a total of 414 fellowship interest surveys were collected from pharmacy students or recent PharmD graduates, and 529 fellowship interest surveys were collected in 2015. A 19% increase in the number of recruitment events corresponded to a 28% increase in student engagement in 2015.

In 2014 the students represented a total of 81 pharmacy schools throughout the country, and in 2015 they represented 92 pharmacy schools. In both years, the largest portion of students was completing their final professional year (31% and 37%, respectively).

In 2014 survey results indicated that for 220 (53%) students, a recruitment event was the first time they had spoken with someone from the MCPHS fellowship program. In 2014 the top three venues through which students learned about the MCPHS Fellowship Program were conferences, career fairs and speaking with current fellows. In 2015 the top three venues were fellowship/residency showcases, the MCPHS website, and conferences. Both years, fewer students were introduced to the program through faculty, alumni, or webinars.

Conclusion: Since 2005, the number of pharmacy schools has increased from 87 schools to now 132 ACPE-accredited schools. As a result, the last decade has seen an unprecedented growth in the number of PharmD graduates compared to previous years. One of the goals of the Committee is to continue to increase awareness of fellowships as a postgraduate alternative to residencies and other traditional pharmacy roles in the increasingly competitive job market.

Recruitment events attended by the MCPHS University Biopharmaceutical Industry Fellowship Program's Marketing and Recruitment Committee in 2014 and 2015 were successful in reaching a large number of students across the country and increased awareness of postgraduate training opportunities in industry. Based on the high level of awareness generated from the Fellowship Program's presence at conferences and career fairs, the Committee will target available resources toward these types of events.

T 29

Risk of Asthma Attacks is Increased in Association With Nonsteroidal Anti-Inflammatory Drugs Adjusting for Season Effects

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Keywords: Aspirin-exacerbated respiratory disease, claims data, self-controlled case series study

Method: Five risk periods were set up based on a timing of period relating to the NSAID prescription start date of each patient. The incidence rate ratios (IRRs) for each risk period compared with baseline periods were calculated with adjustment of seasonal effects as a time-dependent variable.

Objective: To evaluate the risk of acute asthma attacks associated with non-steroidal anti-inflammatory drug (NSAID), a self-controlled case series study (SCCS) using Japanese claims data was conducted.

Result: This study included 31,941 cases, who had experienced acute asthmatic attack on claims data between January 2012 and December 2013. All risk periods (R0 = 7 days before prescription start date, R1 = the prescription start date, R2 = 1–9 days after the prescription start date, R3 => 9 days after the prescription start date, R4 = 7 days after the prescription end date) had a significantly higher risk of asthma attacks than the baseline period. Specifically, the highest risk was observed in R1 (IRR = 93.93 (95% CI: 90.08–97.93)). Small effects of seasonal factors were also observed, especially in autumn (September to November) (IRR = 1.61 (95% CI: 1.57–1.64)), when compared with summer (June to August) in which the risk of asthma onset is considered to be lowest.

Conclusion: The increased risk of asthma attacks was associated with NSAID prescriptions, while season effects which was one of time-dependent effects were relatively limited. The remarkable high risk was obtained at the R1 (the prescription start date) but it could be overestimated due to the reverse causation (the asthmatic attack observed in R1 might occurred prior to the administration of NSAIDs). Since the significant increased risk on asthmatic attack was observed in all risk periods (R0-R4), physicians should aware a possible occurrence of NSAIDs-induced acute asthmatic attack.

T 30

Identifying TPPs and Establishing CQAs to Support Commercial Product Specifications

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Keywords: Commercial product submission, critical quality attributes, efficacy, finished product specifications, hierarchy, manufacturability, new drug, quality, risk-based decisions, safety, target product profile

Method: This study involves the assessment of current practice and FDA Guidance for the process of investigation and definition of a drug from drug discovery through commercial product specification.

Co-Author: Denise L. Miller

Objective: This presentation progresses through the steps in establishing finished product specifications based on desired Critical Quality Attributes from defined Target Product Profiles.

Result: There are no qualitative studies involved. The poster discusses a process as defined by the FDA and applies this process to the evolution of a lyophilized dosage form.

Conclusion: Development of commercial product specifications need to start with identifying the TPP in initial development work, focusing on the CQAs as the product progresses through to commercial manufacturing.

T 31

Comparison of Feature Encoding Methods for Automated Document Classification in Adverse Event Detection

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Keywords: Adverse events, machine learning, natural language processing

Method: Medical article abstracts and case reports were used to train machine learning models to classify documents based on whether or not they suggested an adverse drug reaction. Comparisons were made between bag-of-words, bigram, trigram, tf-idf, and distributed language representation methods.

Objective: Multiple methods for converting the unstructured text of medical research article abstracts into representations suitable for machine learning classification algorithms are tested for their effectiveness in identifying those articles with potentially adverse drug events.

Result: A corpus of medical research article abstracts and case reports that detail patient problems, treatments, and outcomes for a variety of medical disorders and diseases were collected. These documents were classified into two groups based on whether the cause of the problem was likely to be due to an adverse drug reaction or not. Data was prepared by tokenizing each abstract into vectors of single words which were then filtered to remove single-occurrence words, highly common words, and numbers. Encoding the tokenized word vectors for machine learning was accomplished by counting the number of times single words were in each document, as well as two word phrases (bigrams) and three word phrases (trigrams). Another data set was created by weighing each vector using the term frequency-inverse document frequency (TF-IDF) method. This resulted in a sparse, fixed length numeric vector for each document that was used as input for training a logistic regression model for document classification. In addition, we created a model using the distributed language representation method word2vec that produces dense numeric representations of words based on the surrounding context. When turned into a classifier through inversion using Bayes rule, this yielded more accurate results than logistic regression. For this research, we used the open source programming languages R and Python and trained custom models on the Azure Machine Learning platform.

Conclusion: Post-approval pharmocovigilance, or the identification of potential new adverse drug events after drug approval, is a critical goal of the healthcare system. These activities are often mandated by regulatory agencies to ensure the continuous collection of safety data on a drug during normal use and to a more diverse group of patients than is usually possible during pre-approval clinical trials. The continually increasing number of medical journal articles and case studies being published each year has created additional difficulties in monitoring for potential adverse effects in an accurate and timely manner. Numerous data mining and machine learning algorithms have been utilized to reduce the amount of manual expert time required to evaluate a publication for potential adverse effects. However, no standardized methodology has been implemented. The development of distributed language representation methods such as word2vec that utilize neural networks to learn words and their contextual meaning have potential to lead to highly accurate numerical representations of words that can be used for classification models. In this study, we sought to compare distributed language representation methods with more established language processing methodology. The success of distributed language representation methods here suggest that their use should become more common in medical language processing methods.

T 32
Disrupting Clinical Trials in The Cloud

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Keywords: Agile, clinical system, eClinical, EDC, electronic data capture

Method: We will analyse and measure benefits of cloud-based eClinical systems in the following areas: Speed of implementation, User empowerment, Ability to scale up, or down, quickly and Lower cost of technology adoption. We will showcase the adoption of ClinCapture® by medical device or biotech companies.

Objective: This submission describes the benefits reaped by small and mid-sized biotechnology companies who adopt cloud-based eClinical systems to build, run, and manage their clinical studies.

Result: Speed of Implementation: With limited resources and a small clinical departments, it is critical for our users to find an easy-to-implement solution to start and manage the clinical trial process. ClinCapture has a do-it-yourself platform and intuitive drag-and-drop tools to build a study. These build tools, referred to as "studios," allow a data manager to build a study in a matter of days, without any programming experience. Our client Providence Medical was able to build CRFs and deploy the study database in one week. The following week, they trained the sites and started collecting the data. Compared to an average 6 to 8 weeks for a database build, ClinCapture enabled this sponsor to save 4 to 6 weeks.

Autonomy and user empowerment: Switching from paper to EDC requires profound changes on the organization, workflows, SOPs and forms, which are a major deterrent to adoption. For example, CRFs must be redesigned, taking into account dynamic forms and new data entry workflows. Traditional EDC systems require programming and IT skills to build a study and have a steep learning curve for all end-users.

Ability to Scale: A key characteristics of the cloud is "rapid elasticity". It refers to the ability of a cloud service to scale on demand. A mid-study size increase is seamless and doesn't affect performance. In traditional EDC systems, there is a concern as to whether a server can handle workload increases without changing the physical infrastructure, which usually leads to delays and additional costs.

Lower Cost of Adoption: By moving away from Excel files to ClinCapture, the time and cost savings were significant. DigitalizaTXT estimates 40% cost savings compared to paper and 70% time acceleration for data collection and cleaning. Another cause for cost increase using paper is the quality of the data entered on paper CRFs as there is no validation possible at the time of entry.

Conclusion: Relying on cloud-based eClinical systems empowers users while lowering the adoption barriers to traditional EDC systems. With ClinCapture, clinical trial experts now have access at no or very low cost to sophisticated features, a 21 CFR part 11 compliant EDC system, in a validated hosting environment. Clinical trials with a short timeline or low budgets, such as early phase, medical device, diagnostics, nutraceuticals, etc. can now have access to the same level of features sophistication and data quality as the bigger large pharmaceutical companies. It is necessary for sponsors to put controls in place to ensure data quality and integrity throughout their clinical trials. This can be done with paper-based clinical studies, but often with unintended negative consequences, including delays, travel costs and poor data quality. With EDC, edit checks are integrated from the start and are seamlessly activated during data entry, ensuring that the sites can address most issues as they occur. In the cloud, thanks to powerful, automated edit checks, it also results in fewer human errors and therefore higher data quality, which is one of the top performance indicators for drug developers. The ability to closely cooperate with all the stakeholders optimizes subject flow, experimental design and execution, and ultimately enhances data quality. Having access to a validated cloud-based EDC tool that requires no resource for infrastructure, maintenance and updates, allows us to focus on the business of drug development.

Despite low pay-as-you-pricing models, cloud-based businesses actually generate a higher profit margin through cloud automation, multitenancy, and a lower cost of sales. Marc Benioff, the CEO of Salesforce, projected over 10 years ago that all software would be eventually deployed into the cloud. We believe the time has come for eClinical Software to make that transition.

T 33
Utilization of National Webinars to Reach Students for Educational Opportunities: A Two Year Analysis

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Keywords: Education, fellowship, pharmacy, students

Method: Webinar flyers were sent to all ACPE-accredited pharmacy schools and distributed at fellowship recruitment events in 2014 and 2015. Registration forms captured academic affiliation and anticipated graduation year. Geographical reach was matched to APhA-ASP regions and compared between years.

Co-Authors: Christina Fang, Sarah Stelzleni, Amy Monpara

Objective: To assess the reach of national webinars held in Fall 2014 and 2015 by the MCPHS University Biopharmaceutical Industry Fellowship Program aimed at improving awareness of Post-PharmD fellowship opportunities within the pharmaceutical, biotechnology, and medical device industries.

Result: In 2014, 373 participants registered for the 2 webinars in the fall. Students in their final professional year (anticipated graduation: 2015), represented the largest portion of registrants (46%, n=171); the remainder of registrants were on track to graduate in 2016 (24%, n=90), 2017 (16%, n=58), 2018 (12%, n=46), 2019 (0.5%, n=2), or had already graduated (2%, n=6). Students from schools in all regions of the country registered: Southeast (20%, n=75), Mid-Atlantic (17%, n=62), Great Lakes (16%, n=58), Southwest (16%, n=60), Northeast (15%, n=57), South Central (13%, n=50), North Central (3%, n=10), Northwest (<0.5%, n=1). 62 individual pharmacy schools were represented. Of all registrants, 200 (53.6%) attended the live webinars.

In 2015, 597 participants registered for 2 webinars in the fall. Once again, students in their final professional year (anticipated graduation: 2016) represented the largest portion of registrants (58%, n=346); the remainder of registrants were on track to graduate in 2017 (21%, n=125), 2018 (13%, n=76), 2019 (6%, n=38), or had already graduated or were earlier in their education. Once again, students from schools in all regions of the country registered. The majority of registrants attended schools in the Mid-Atlantic (29%, n=171) followed by the Northeast (22%, n=133), Southeast (15%, n=92), Great Lakes (14%, n=81), Southwest (10%, n=60), North Central, (4%, n=24), South Central (4%, n=24), and Northwest (2%, n=12). 94individual pharmacy schools were represented. Of all registrants, 360 (60.3%) attended the live webinars. Total registrants increased by 224 (160% increase) from 2014 to 2015. For both years, as expected, students in their final professional year made up the largest portion of registrants. All regions were represented in both years reviewed, however the majority regions changed from 2014 to 2015.

Conclusion: The use of printed and electronic informational flyers to inform students of the webinars and postgraduate opportunities both increased registration and encouraged the participation of many students from a large number of pharmacy schools across the nation in 2014 and 2015. Webinar registration increased by 160% from 2014 to 2015. Students in their last professional year of pharmacy school (P4), actively pursuing postgraduate opportunities, comprised the highest number of registrants in both 2014 and 2015. Following the 2014 webinars, it was shown that webinars have the potential to be an effective tool in increasing students' knowledge regarding postgraduate fellowship opportunities. However, a notable concern of this initiative was the modest live attendance rate of the webinars. In 2014 approximately half of all registrants attended at least one of the live webinars. Despite the improvement in conversion of registrants to live webinar attendance observed from 2014 to 2015, additional strategies to bolster live webinar retention should be explored to maximize the educational impact of this initiative for future iterations.

Based on the impact and reach of these educational webinars the MCPHS University Biopharmaceutical Industry Fellowship Program Recruitment and Communications Committee will continue to utilize national webinars in upcoming years as a marketing tool targeting PharmD students exploring postgraduate opportunities.

T 34
Signal Analysis of Adverse Drug Reactions: Signal Detection/Evaluation Method Formulation Using Important Risk Visualizer™

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Keywords: Adverse drug reaction, pharmacovigilance, risk management, signal detection, statistical analysis

Method: The data from the in-house safety database was installed into the "Important Risk Visualizer" ™, a registered trademark in Japan (IRV), the statistical parameters were calculated and ADRs were categorized by the analysis template based on the evidence-based and public health-based scores[1].

Objective: We have created an original signal detection/evaluation method for adverse drug reaction (ADR), based on multiple statistical parameters, because practical utilities of medical product ADR signals have not been fully examined in post-marketing.

Result: The number of ADRs which may have any causality with each product spanned a few dozens – several hundreds in the safety database, despite the importance of prioritizing ADRs in order to enforce early and effective measures based on accurate the signal detection / evaluation. We calculated the 4 statistical parameters (Reporting Odds Ratio (ROR), Proportional Reporting Ratios (PRR), Gamma-Poisson Shrinker (GPS) and Bayesian Confidence Propagation Neural Network (BCPNN)) and examined significance of them. ROR and then GPS were relatively likely to be significant rather than PRR and BCPNN, regardless of numbers of cases.

By the above methods, those ADRs were effectively categorized using the above two scores ranging one to 100, each with three input variables, in terms of the strength of evidence and the potential public health impact. A certain number of ADRs were categorized as "High priority", since the both scores of them were beyond the thresholds.

Most of these ADRs with "the High priority" were confirmed to be notified as the Safety Specifications in the Risk Management Plans and/or as the cautions in the package insert of each product.

Conclusion: These results demonstrate that ADR signals are practically available for pharmacovigilance activities. This original method for ADR signal detection/evaluation, using multiple statistical parameters, through IRV, may be potentially useful for the proactive and accurate ADR risk management.

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1) Patrick Waller, Emma Heeley and Jane Moseley. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data. Drug Safety, 2005.

T 35

Bridging Study Evaluation in Taiwan

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Keywords: Bridging study, Taiwan

Method: Taiwan Center for Drug Evaluation (TCDE) has reviewed the technical dossiers of BSE applications since 2004. Cases with Asian data gained waiver or non-waiver of bridging study are analyzed. We also analyze the deficiencies of the non-waiver cases.

Objective: Bridging study evaluation (BSE) is a process required before or with NDA submission in Taiwan. The purpose of BSE is to evaluate if there is any ethnic difference. The study aims to evaluate the relationship between BSE results and the present of Asian clinical and/or PK data in the BSE package.

Result: More than 400 BSE applications were submitted since 2004. The percentage of cases with Asian data increased from 54% to over 80%. Overall, about 80% of cases with Asian data gained waiver of bridging study. For the non-waiver cases with Asian data, frequent deficiencies include: the Asian data are too limited to evaluate ethnic difference; the Asian PK and/or clinical data shows ethnic difference; and improper design of the Asian study.

Conclusion: There is a trend of more and more Asian data being submitted. Cases with Asian data have a higher probability to gain bridging study waiver.

T 36

Reduce Training Redundancies to Improve Clinical Trial Efficiency

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CNS Healthcare

Keywords: Improve clinical trial efficiency, reducing redundancies

Method: CNS Healthcare Orlando, Jacksonville, Memphis. Initial rater training required by a protocol and performed during 2015 at these sites.

Objective: Redundant training continues to be a significant and unnecessary burden for the research sites that are otherwise most efficient and proven to be highly successful at conducting clinical trials, specifically those with years of experience in clinical trials.

Result: Chart 1 shows total number of raters across the three sites who received initial rater training for a protocol in 2015. There were 28 total raters. Of those 28, 16 were required to do repeat training on rating scales during the year. Chart 2 shows the number of times (greater than one) a rater had to complete training for the same scale. Forty three different times a rater completed training on the same scale twice, and twenty three times a rater completed training on the same scale three times. This goes all the way up to three different people who completed training on the same scale ten different times. In total, repeat training was done 210 times across 16 individuals. And this data is for the year 2015 only – the same process repeats itself continuously throughout each year. Chart 3 provides an example of one rater, the scales this rater was required to repeat training on, and the number of times the repeat training was required. This particular rater repeated training on 13 different scales, some multiple times, for a total of 35 repeats. Again, this is one individual rater for one calendar year. As seen in Charts 4 and 5, the Columbia Suicide Severity Rating Scale© (C-SSRS) is an example where progress has been made, although accidentally. Because there is only one rater certification available, and one certificate given (that lasts for a period of two years), sponsors sometimes accept a rater's current certificate instead of requiring the rater to repeat the training ad infinitum. For eight protocols, new C-SSRS training was required – once for 3 individuals, twice for 3 individuals, three times for 5 individuals, four times for 2 individuals, and five times for one individual. However, the sites participated in an additional 12 protocols during this time that required other initial training but the C-SSRS training was not required if the rater had a current certificate.

Conclusion: Repeat training was done a total of 210 times at these three sites over the course of one calendar year. If we assume an average training time of 30 minutes (and it is very often more – some of the scales require web-based modules and then recorded live interviews to be assessed by the rater certification company), that is 105 hours (or over 13 days) taken from activities such as recruitment, completing subject visits, entering EDC data. These are hours added on to the time it takes to complete the lifecycle of a clinical trial.

T 37

Use of a Mobile Robot to Facilitate Long Distance Professional Development Meetings For Post-Doctoral Fellows

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Keywords: Continued education, distance learning, fellowship, innovation, post-doctoral, professional development, robot, technology

Method: The Professional Development and Technology Committees conducted a needs assessment and proposed utilizing a mobile robot. The Double Robot offers a telepresence, allowing West Coast fellows to feel more connected and engaged by providing a remote-controlled physical presence as well as a live feed.

Objective: The Rutgers Pharmaceutical Industry Fellowship (RPIF) Program continues to grow and now has a significant presence on the West Coast. There has been an increased need to find a solution to incorporate West Coast and traveling fellows into the professional development series taking place at the University.

Result: The robot was piloted at a professional development/seminar series. It was able to maneuver in the seminar space and became a part of the live workshops and applied learning activities, while displaying a live audio/video feed of the West Coast fellows. The process of conducting meetings with personnel off site was seen as a valued skill set for training industry fellows. A preliminary assessment found that the West Coast fellows felt more engaged with the activities and that the fellows on the East Coast did not find the robot to be overly intrusive or distracting.

Conclusion: The use of the mobile robot has facilitated interaction among post-doctoral fellows on the East and West Coasts. A formalized survey is being conducted to further evaluate the level of engagement the robot provides for remote seminar attendees.

T 38

Electronic Document Presentation During a Japan PMDA Inspection

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Keywords: Inspection readiness, J-NDA, Japan PMDA inspection, Japanese regulations, PMDA, regulatory audits

Method: In 2014-2015, Gilead Sciences participated in its first two PMDA Inspections in Japan. The first PMDA inspection was paper-based in which all documents were printed in advance. For the second PMDA inspection, documents were prepared and presented electronically to inspectors.

Objective: The objective of this case study was to develop an effective, electronic method of compiling, organizing, and searching for documents during a Japan PMDA Inspection.

Result: As required for each J-NDA, PMDA inspectors spend 1-2 days conducting a document-based inspection of the sponsor. The turnaround time is very rapid, with documents being presented within seconds of the request.

Gilead's first PMDA inspection was paper-based. All documents associated with the study were printed, including all Controlled Documents (SOPs, Work Practices, Forms), all documents in the TMF, as well as informal documents such as emails or trackers.

Preparing and organizing the documents into binders were challenging and time-consuming. The number of binders was unexpectedly high: a total of 200 binders (equivalent of 55 feet tall, if stacked). All binders were assembled in the US, and during shipment to Japan, some binders were damaged or lost. Last-minute changes were difficult to accommodate. During the inspection, the binders were difficult to manage; the binders' bulkiness made it hard to navigate to documents quickly. The large number of binders and paper documents created clutter on tables and throughout the room.

4 months later, Gilead's second inspection was held, and the Regulatory team confirmed that PMDA would accept electronic documents during the inspection. A predetermined folder structure and naming convention were developed for all department areas to follow. The complete Table of Contents (TOC) was printed into mini-booklets that corresponded with the folder structure. All 6,500 documents had unique number codes based on the folder organization.

3 laptops were prepared with all documents, and logistics were developed for presenting documents requested—without allowing perusal of other documents by inspectors. [1] The Interviewee and Navigator consult the TOC to identify the electronic folder number of the document (e.g. E01.02.01). [2] The Navigator opens and checks the document on the laptop's primary screen. [3] The Navigator drags the document to the external monitor so that the inspector can review the document.

Conclusion: Instead of 200 binders full of paper documents, only 3 laptops were needed to store 6,500 files--about 15 GB total. The flexibility of electronic documents allowed for last-minute changes and for copies to be given to interviewees to prepare. Electronic documents resulted in an organized workspace during the inspection, without the clutter of binders and papers.

The Navigator role resulted in efficient, smooth delivery of documents requested by inspectors. Delivering documents requested by inspectors was more efficient, and a faster turnaround could be achieved than with the paper-based documents. Although all documents were loaded on each laptop, the logistics of presentation prevented the inspectors from viewing other documents that weren't requested.

The electronic method of presenting documents to PMDA inspectors was recognized as a success by all participants, and Gilead will use this method for all future inspections.

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T 39

Bangladesh: A New Frontier for Global Clinical Trials

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Keywords: Clinical trials, non-traditional sites, active lupus nephrit

Method: Over 80 sites from 23 countries are participating in the AURA study in lupus nephritis(LN), a rare disease requiring the use of a global approach to recruitment. Patients were required to have a local kidney biopsy, centralized ECG testing, along with PK sampling and blood work over 50 weeks.

Objective: This abstract details the development of new GCP standardized clinical investigator sites that have diverse disease profiles and large patient base in a country traditionally overlooked for global studies. This effort involved the creation of a SMO to assist and oversee Investigator efforts.

Result: Prior to study patient enrollment, sites were chosen based upon clinical expertise in this rare disease. Study teams were created and GCP training was conducted by the CRO among all staff involved in the study. A refresher course was conducted during study participation to ensure GCP standards were maintained. The total time required in Bangladesh to obtain central as well as the site IRB approvals was 4 months. One month was required for Import permits by the Directorate General of Drug Administration (DGDA) and export of biological samples by the Ministry of Commerce. Although the initial country target was to enroll a maximum of 25 patients from Bangladesh, quality in clinical care and ensuring the ICH-GCP guidelines were closely and constantly maintained allowed for an increase in countrywide enrollment.

Among the 7 Asia-Pacific countries, the proportion to the patient screened to randomization indicates a higher patient yield in Bangladesh - 46/62 (74%); followed

by Philippines 44/67 (66%) and Thailand 13/19 (68%). There were regular country-wide IRB (including members from local site IRBs) safety review meetings held to ensure patient safety and compliance with ICH-GCP guidelines. Any protocol deviations required explanations from investigators. A proper courier service was established ensuring sample shipment as per study schedule, and ensuring shipment clearances on time at customs resulting in no delay or halt of sample exports. Repeated renewal of IP import through DGDA were done without any interruption.

Conclusion: 80% of clinical studies fail to meet enrollment deadlines, and 50% of sites enroll 1 or no patients. Effective therapies remain unavailable to almost all patients with rare diseases. Yet, studies requiring FDA submission need to reexamine global approaches. Consideration of Bangladesh as a part of a global study involved intensive efforts to clarify study conditions and investigator qualifications, along with study supports ensuring ICH-GCP compliance. Sponsor/CRO review included the use of icddr,b (International Center for Diarrheal Diseases Research, Bangladesh) globally known for their invention of ORS to play a key role in Investigator oversight.The icddr,b IRB has the FWA (Federal Wide Assurance number from USA) and is approved by a special act of the Government of Bangladesh to be an independent body to approve and to conduct clinical trials in Bangladesh. This IRB meets monthly and in occasion arranges special meeting for expedited CT reviews. Bangladesh was the highest patient recruiter overall. The highest number of patients randomized following screening in Bangladesh (74%) not only ensures availability of such patients but also indicates the clinical experience of the investigators to pick appropriate cases early on as per the study inclusion criteria. That results in faster recruitment, saving unnecessary investigations and reducing overall study cost.

Bangladesh a country of over 160 million with many treatment naïve patients; increased number of lifestyle diseases are emerging with the change of the economy of the country from low to middle income country. Young physician Investigators have their medical training in English, and are trained in the same standard as UK Investigators. These combinations can be a potential game changer for international clinical trials and global CROs to explore in this newly emerged clinical research country.

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T 40

What's in a Number? Differences in Enrollment Rate Calculation Methodologies for Clinical Trial Planning

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Keywords: Data-driven enrollment projections, enrollment projections, enrollment rates, feasibility

Method: For all studies with evaluable metrics conducted at Quintiles in the past 5 years, we compared internally calculated enrollment rates with enrollment rates determined using available public data.

Objective: Understand limitations associated with using publicly available data to estimate prior trial recruitment rates.

Result: Calculating enrollment rates using individual site and country enrollment periods provides different recruitment rates than available through public sources. In some cases these differences in rates are substantial and could have significant implications on enrollment assumptions associated with clinical trial planning.

Conclusion: Using prior data to estimate enrollment rates is a hallmark of planning for clinical trials. However, the specific methodology and sources of study milestones used to calculate such rates can lead to substantial differences in estimates used for study planning. Depending on the available information regarding numbers of and location of sites, countries, study timelines and other variables, enrollment rates may be substantially different than what was actually experienced in the study. The implications of this are inaccurate projections for study timelines, which may impact budget forecasting, study resourcing, and project management, as well as any services that are associated with patient accrual into clinical trials.

T 41

Enabling Global Regulatory Submission Project and Portfolio Management

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Keywords: Approvals, global, portfolio management, project management, registrations, regulatory submissions, technology

Method: Development of a Portfolio Submission Project Management (PSPM) tool based in Microsoft Project Server with integrated connections to an Appian portal interface.

Co-Author: Zach Huggins

Objective: Enable global regulatory submission portfolio planning and project management through integrated processes and innovative technologies.

Result: PSPM Tool and supporting processes deliver the planning capability to support global regulatory submissions. This includes several key capabilities, including: ability to develop a Central Plan (with components authored at headquarters) linked to a Regional Plan (with modified, translated, or locally authored components for a particular country filing). Enables a single location for planners to update high-level milestones (provides visibility into the submission lifecycle) and component-level planning information (the documents and subtasks required to execute the submission).

Provides a means for Country Regulatory Affairs staff to access documents authored at HQ, and also provides the capability for Country RA staff to be assigned and complete tasks (via interaction with the RIM Portal).

As a result of implementing PSPM, we have the ability to view the entire portfolio of regulatory submission work, including the lifecycle status of each submission (Plan Baselined, Plan Complete, Publishing Complete, Agency Submission, Agency Decision), the planned and actual dates achieved (with reasons for delayed milestones), and drill down capability to review the specific documents provided for each country regulatory filing (and the corresponding headquarters-authored document for documents which are modified, translated, or redacted at the local level).

The output of PSPM is a work order for the publishing team to assemble and release the submission to the health authority, which doubles as an archivable report with links to the specific documents used in the submission.

Business impact is transparency and visiblity of each regulatory filing status across the portfolio, enabling robust portfolio management and ultimately prioritization and resource management decisions. In addition, the tool and process drive significant impact in increasing 'right-first-time' quality and reducing cycle time and rework for filings in major markets and around the world.

Conclusion: Implementing PSPM tool has already had several benefits - planners benefit from a common platform for entering milestone information and project managing submission components, countries benefit from greater visibility into upcoming work and the ability to provide input during the planning stages (rather than reworking documents sent to them by HQ), content authors benefit from having a dashboard of assigned work and a straightforward method by which to provide their completed documents, and regulatory affairs management benefits from the visibility and analytics of all regulatory submission activity.

PSPM tool has integrated several disparate activities conducted by various roles within Regulatory Affairs Operations - it has made their jobs easier, the published submissions more consistent, and the process of planning and executing submissions around the world more transparent and more efficient.

T 42

Talimogene Laherparepvec: Advanced Therapy Medicinal Product (ATMP) – A Distinct Risk Management Plan

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Keywords: Advanced therapy medicinal product, oncolytic immunotherapy, pharmacovigilance, risk management plan

Method: When preparing a risk management plan for an advanced therapy medicinal product (ATMP), EMA and EMA Guidance on Safety and Efficacy Follow-up -Risk Management of Advance Therapy Medicinal products were consulted on possible risks in addition to the review of clinical and pre-clinical data.

Objective: To present a distinct risk management plan for a first in class oncolytic immunotherapy that is based on a live attenuated virus and the challenges associated in developing a robust plan to minimize and mitigate the risks associated with the viral nature of this product.

Result: The marketing authorization holder (MAH) incorporated additional risk minimization activities such as patient alert cards, physician education booklet, patient safety brochure, managed distribution, and traceability into a risk management plan that met the requirements of the EU RMP guidance for ATMPs. A unique risk to the patient as well as the public health was the potential risk of secondary transmission, based on the viral nature of talimogene laherparepvec. The EU Summary of Product Characteristics (EU SPC) and additional educational material include measures for minimizing risks such as accidental exposure and secondary transmission. In order to monitor the potential risk of talimogene laherparepvec transmission, in HCP, patients, and close contacts reporting suspected herpetic lesions, a special qPCR testing process was developed to test for talimogene laherparepvec DNA with a follow-up questionnaire in addition to a post-marketing observational study to solicit follow-up of patients for herpetic illness and potential for transmission. Additional risk management elements under the ATMP classification included the incorporation of a managed distribution and traceability program. The objective of this program is to ensure that institutions (including HCPs) using talimogene laherparepvec are trained on the proper storage and handling requirements due to the unique nature of this product. Most importantly, institutions/HCPs should report adverse drug reactions including batch (lot) level information. Each vial has a peelable label to be placed in the patient chart to ensure traceability between the patient, treatment received, and treating center.

Talimogene laherparepvec has been approved in US, EU and other countries. To date the MAH has not received any reports of secondary transmission.

Conclusion: Talimogene laherparepvec is a novel live attenuated oncolytic immunotherapy based on the wild-type herpes simplex virus 1 (HSV-1) genome. It is derived from the HSV-1 strain JS1 from which 2 genes, infected cell protein (ICP) 34.5 (gene responsible for neurovirulence) and ICP47, were functionally deleted. The functional deletion of ICP34.5 results in tumor-selective replication, and deletion of ICP47 enhances antigen presentation. Deletion of ICP47 also increases the expression of the HSV US11 gene, which enhances virus replication in tumor cells. The viral thymidine kinase gene, responsible for phosphorylating acyclovir to acyclovir-monophosphate, is maintained, rendering talimogene laherparepvec sensitive to anti-viral therapy. Talimogene laherparepvec also contains the gene coding for human granulocyte macrophage colony-stimulating factor (GM-CSF) so that GM-CSF is expressed locally upon viral replication. Talimogene laherparepvec has recently been approved in the EU, US, and AU. In the EU, talimogene laherparepvec is considered an ATMP and one of the unique aspects of this first in class, oncolytic therapy, are the associated identified and potential risks that required the development of a distinct risk management plan (RMP) to meet the ATMP classification guidelines in the European Union. Due to the viral nature of this product, special emphasis on the risk of transmission to unintended individuals, such as close contacts, accidental exposure, disseminated herpetic infections in the severely immunocompromised and potential harm to fetus or neonate during pregnancy is provided in the RMP. These risks required the MAH to include comprehensive risk mitigation and minimization measures through succinct labelling and pharmacovigilance activities.

Co-Author: Deborah Arrindel (Arrindell, A)

T 43

Evidence for Empirical Power Law Scaling in Adverse Event Profiles

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Keywords: Adverse event profile(s), AEP, MedDRA, power law, scale invariance, Zipf's Law

Method: The author examined spontaneous adverse events from large, de-identified sponsor internal post-marketing safety datasets (ranging between approximately 48,000 to 250,000 events per molecule) for 4 marketed products for anti-infection, thrombolysis, oncology treatment and inflammation.

Objective: To evaluate recent published claims (Chen and Bryan 2015) that post-marketing adverse event data demonstrate empirical power law behavior.

Result: All adverse event data for each molecular product was summarized and ranked in decreasing order of the proportion of total events. The data was then transformed to log-log scales in order to estimate the non-linear decay constant for each respective molecule, using the SAS-JMP 11.1.1 statistical software. Finally, the AEPs for each molecule were plotted together on the same graph to visually determine if there was similar power-law behavior across molecules.

All evaluated AEPs demonstrated similar non-linear power law behavior. Specifically, despite the variation in mechanisms of action, dose, or route of deliver (e.g., Intravascular, Subcutaneous, Oral, Intravitreal, etc.) all AEPs demonstrated similar visual and numeric behavior with proportionality constants ranging between 0.03 and 0.08, and non-linear decay constants ranging between approximately -0.5 and -0.7. Visually, all AEPs could be superimposed on the same graph with one equation fitting all molecules with proportionality constant = 0.06 and decay constant = -0.7.

Based on the evaluation of spontaneous and clinical trial adverse event reports for molecules from this Sponsor safety database, these results support the findings in recent publications that adverse event profiles demonstrate statistical power law behavior. In addition, this behavior appears to be robust across therapeutic class, target patient population, mechanism of action, or delivery mechanism.

Conclusion: This investigation supports the finding of empirical statistical power law behavior in adverse event profiles and further suggests that this behavior is similar across therapeutic domains, molecule type, and the product lifecycle. Similar to empirical power law behavior in other areas of science (e.g., "Zipf's Law" in human languages, distribution of lunar crater sizes, allometric scaling in biology, and Pareto income distributions), this behavior suggests an underlying pattern and predictability in the reporting and accumulation of adverse events from patients and their treatments.

T 44

Current Japanese Diabetic Mellitus Prevalence and Glucose Clamp Studies for Global Anti-Diabetic Development

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Keywords: Anti-diabetics, diabetic mellitus, glucose clamp, Japan

Method: We reviewed 27 Japanese glucose clamp studies from 1997 to 2016, and investigated the studies by the type of subjects, clamp, investigational drugs tested, and by the clamp duration. We also planned and conducted a hyperglycemic clamp study in healthy Japanese male subjects to verify the procedure.

Objective: As the prevalence of Diabetes Mellitus is consistently increasing in Japan, more and more anti-diabetic drugs are being tested, targeted for this potentially big market. To conduct safer and more efficient clinical trials for hypoglycemic drugs, we reviewed glucose clamp studies conducted in Japan.

Result: We conducted over 250 anti-diabetic studies as of Jan. 2016. Among these studies, 23 studies were conducted using the auto glucose clamp technique. We investigated these studies by the type of subjects (Type 1 Diabetes Mellitus (T1DM) patients, Type 2 Diabetes Mellitus (T2DM) patients, or healthy volunteers), clamp (Hypoglycemic, Euglycemic, or Hyperglycemic), type of investigational drugs tested, and by the clamp duration. A total of 576 subjects were enrolled for the glucose clamp studies, including 151 T1DM patients and 50 T2DM patients.

Our glucose clamp procedures were performed from 2 hours in length to as long as 36 hours in length depending on the study design, and were well tolerated by all subjects. The investigational drugs that were tested using glucose clamp techniques varied from insulin inhalation to oral anti-diabetics.

Hypoglycemic glucose clamps and hyperglycemic glucose clamps were approved by our central IRB without any issues, and conducted safely in T2DM patients.

The data from the clinical research in healthy subjects verifying the study design and procedures of future hyperglycemic clamp studies showed that we were able to maintain a hyperglycemic condition for substantial study periods in healthy Japanese volunteers safely, and also that both insulin phase 1 and phase 2 increases were clearly detected in healthy Japanese volunteers.

Conclusion: In this study, we reviewed and evaluated all glucose clamp studies that used an artificial pancreas (STG-22, Nikkiso Co. Japan)conducted at SOUSEIKAI over the last 20 years.

Hypoglycemic drugs are potentially risky when administered to subjects during clinical trials, and so it is essential that special attention be paid to monitor and, if needed, treat subjects accordingly.
By using the glucose clamp technique, it is safer and more efficient to keep a subject's blood glucose levels at a desired level for a certain amount of time.

Also, by choosing one of the three methods of glucose clamp (Hypoglycemic , Euglycemic, or Hyperglycemic), it is possible to evaluate not only the PD of insulin preparations, but also insulin sensitivities/ resistances, insulin secretory properties, and glucagon secretion in any type of diabetic patient or healthy subject.

Although there are generally fewer T1DM patients in Japan when compared with other countries, we were able to conduct 7 glucose clamp studies in TIDM Japanese patients over the last 10 years, involving studies of up to 36 continuous hours on the glucose clamp for various types of insulin preparations. Our data suggested that it is important to control subject blood glucose levels thoroughly for the targeted level, especially during the night when a 36 hour-long glucose clamp is used; also it is crucial to adequately handle both rapid blood glucose level changes as well as frequent blood sampling when the glucose clamp studies for ultra rapid acting insulin preparations were used. We concluded that by using the glucose clamp technique, we can safely, accurately, and continuously monitor the effectiveness of hypoglycemic drugs, among others, in clinical trials.

Furthermore, from the results of our hyperglycemic clamp research in healthy volunteers, it is suggested that the hyperglycemic glucose clamp technique is useful for evaluation of not only insulin preparations, but also various oral antidiabetic drugs.

T 45

Evolution of e-System to Support Needs of Agile Pharmaceutical Company: A Case Study of Growing Together

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Keywords: Big data, e-system

Method: A case study based on real system implementation in global pharmaceutical company.

Objective: Pharmaceutical companies and CROs are facing growing challenges of effective management of Big Data. Integrated approach supported by case studies will be presented in our talk.

Result:

1. Key integration challenges are focused on e-systems for just storing data, investments into the future are usually unclear, the cross-functional nature of big data itself.
2. Pharma – CRO – Site. New Big Data Paradigm, what does it give us? Adopting best industry practices, better data, solving problems quickly.
3. E-System purpose: data integration, optimization of R-Pharm business processes, and as the result - quality and productivity increase.
4. Core of the system, starting with the basics, the critical modules of the system. Then deep dive into system development with systems' applications and business processes automation.
5. An example of one automation of one business process: goals, timelines, resources.
6. System overall development.
7. Case studies with Investigator and site management and PV modules.

Conclusion: Close partnership in e-system development and implementation are for success confirmed by a real life example.

T 46

Do Environmental Parameters Influence the Prediction of the Placebo Response?

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Keywords: Analgesia, clinical trials, neuropathic pain, placebo, predictor

Method: PNP patients were given a blinded placebo (presented as "new treatment") in addition to their regular analgesic treatment. They were randomized to follow a "Influenced" or Sham procedures designed to assess the environmental factors that may influence the placebo response when administrating a drug.

Objective: This proof-of-concept study on peripheral neuropathic pain patients investigates the potential influence of the investigator on the placebo response in RCTs while manipulating different variables, including patient expectation, conditioning and prior experiences, observational and social learning.

Result: 41 completed the study. They suffered from PNP based upon medical examination for at least 6 months. The sex ratio was 21:22 (49/51%) for males and females, respectively. The mean age of the patients was 57 years old (SD=11.4). The median history of PNP was 7.2 years.

The 20 patients in the "Influenced" group followed the studied placebo-reinforcing procedure consisting of positive expectation directed information about the placebo in the form of a video. The patient then underwent pre-treatment heat pain stimuli. After the pain stimuli, patients were given their first placebo capsule and underwent a new heat pain conditioning approximately one hour after dosing. The post-treatment heat pain conditioning protocol was intentionally modified from the pre-treatment, one as the mean intensity was reduced to induce the patient's belief in analgesic efficacy.

The 21 patients randomized to the "Sham" group followed the Sham procedure consisting of no expectation of improvement, neutral social observational learning and no modulation of pain stimuli. Those patients watched a video presenting only neutral properties of T4P1001 drug (placebo). Both groups were given capsules to be taken twice a day over 4 weeks as add-on therapy to their regular analgesic. The weekly mean of the average pain score (APS; computed on a 11-point numerical rating scale) at baseline was 5.3. After four weeks of placebo treatment, across groups, 12 patients (30%) had an important decrease of their average pain of more than a 20% from baseline. Overall, the mean APS decreased significantly by 0.7 (effect size=-0.50; p-value=0.0047) to 4.6. The 20 patients in the "Influenced" group had a significant decrease by 0.9 (95%CI=[0.2,1.6]; p-value=0.0167) of their mean APS. The decrease was less important in the "Sham" group with a decrease by 0.5 (95%CI=[-0.2,1.1]; p-value=0.12785). However, the difference of decrease between the two procedures was not significant (p-value=0.4162).

Conclusion: The global magnitude of the mean placebo effect was considered as moderate but in accordance with published meta-analysis in chronic pain. This relatively mild placebo response could be explained by the mode of administration. The placebo given as an add-on therapy may have decreased the expectation associated to efficacy of the treatment. Yet, one third of the patients demonstrated a strong placebo response.

If the patients following the "Influenced" procedure seemed to have a more important decrease of APS, they were not significantly different from the "Sham" group. This marginal difference 0.9 vs 0.5 (respectively for influenced and sham group) should be put into perspective with individual variation. Indeed, both groups had a wide range of placebo responses and a high variance. The "Influenced" group responses ranged between -2.0 and 4.4 (sd=1.49). The "Sham" patients were comprised between -1.1 and 5.4 (sd=1.43). This high individual variation combined with small sample sizes could explain better the likelihood of an observed center effects than a true investigator bias.

To control the increasing placebo response affecting the assay sensitivity in RCTs, many study level factors have been studied such as number and type of patients, study design and outcome measurement. An other aspect investigated here on peripheral neuropathic pain patients is the potential influence of clinical investigator sites on the placebo response. We tried to mimic and maximize it while manipulating the patient expectation and conditioning through two different procedures. Our results, however, show that the "true" site effect is marginal compared to the intrinsic placebo fluctuations. This advocates for a better characterization of the individual placebo response. The prediction of the placebo responders may be used in RCTs to stratify patients within groups, and thereby to increase the assay sensitivity.

T 47

True Globalization of the PSMF and Why It's a Useful Tool for Non-EU Pharmaceutical Companies

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Keywords: Company oversight, oversight, pharmacovigilance, PSMF, PV systems, QPPV oversight

Method: Development and ongoing maintenance of 18 Global Marketing Authorisation Holders PSMFs, created by a specialist pharmacovigilance service provider, following the introduction of Good PV Practise (GVP) legislation into the EEA 2012. Reviewing against all company procedures and GVP guidelines.

Co-Author: Natalie Smith

Objective: Demonstration of how the Pharmacovigilance System Master File is a useful tool for a company to ensure global pharmacovigilance quality and compliance, irrespective of the size, type, and location of the marketing authorisation holder.

Result: The data checklist enabled collection of data across all departments for inclusion into the Pharmacovigilance System Master File. The collated data into a central repository revealed, previously unknown information to key stakeholders within the company. The PSMF provided oversight to senior management within the company and demonstrated where there were potential gaps, areas for improvement and where departments were functioning well with regards to quality and compliance. This pharmacovigilance tool had aided preparation for company regulatory inspections, and ensuring all topics with pharmacovigilance have been addressed appropriately. Since the introduction of the PSMF legislation, we have developed the PSMF tool which has been the subject of a number of successful regulatory audits and inspections.

Conclusion: The Pharmacovigilance System Master File, was demonstrated to be a useful tool for collating information within a company across multiple departments and sites, which would not normally communicate resulting in a central repository. It allows strategic project plans to be developed to ensure continuing improvement and maintenance of a robust pharmacovigilance system. Companies should consider, irrespective of size or location adopting the pharmacovigilance system master file into their companies as a global tool. A complete robust PSMF will enhance the smooth flow of a regulatory audit or inspection, and will instil confidence in an auditor or inspector that the MAH has complete oversight of their pharmacovigilance system. In addition, the PSMF ensures all departments work together to ensure full protection and safety of patients using their products. It aids smooth transition for acquisitions and due diligence and collaboration with partners and vendors. It aids in the understanding of the complex legislation within the EU and stringent requirements concerning safety; example of this include full oversight of a company's vendors, Qualified Person responsible for pharmacovigilance and National Persons responsible for Pharmacovigilance. For any companies considering submission of a marketing authorisation application in the EEA, the adoption of a global PSMF will ensure a smooth transition into European markets here.

T 48

Best Practices for Development or Migration of Patient-Reported Outcome Measures for use on Multiple Data Collection Modes

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Keywords: Best practices, electronic patient-reported outcome (ePRO), patient-reported outcome (PRO) measures

Method: The ePRO Consortium members collaborate pre-competitively to further eCOA (e.g., ePRO) science, including supporting/conducting research and defining best practices. These best practices focus on PRO instrument development and migration principles that consider the range of data collection modes.

Objective: To describe best practices developed by the Critical Path Institute's ePRO Consortium for instrument development and electronic migration of patient-reported outcome (PRO) measures to ensure data comparability across data collection platforms and enable use in the broadest range of clinical trials.

Result: A number of considerations factor into the selection of data collection modes for PRO instruments, including functional limitations of target patient population, data collection setting (field-based or site-based), length of the instrument, and translatability. However, whether developing a new PRO instrument or migrating an existing one to an electronic data collection mode, there are specific considerations to ensure consistent implementation across a range of platforms. The following are examples of the considerations to be addressed.

Instructions: Should be mode agnostic (unless using an interactive voice response [IVR] system), clear and succinct, with minimal changes to make sense on an electronic platform (e.g., 'select' instead of 'circle').

Items: The text should be concise and self-contained. All information that the respondent must consider when formulating a response (i.e., item text, recall period, definitions) should be included on a single screen.

Response Options: Response scales require special consideration, particularly when designing an instrument for use on multiple electronic platforms. When designing for screen-based devices (e.g. handheld, tablets or Web), the hit spot for each response option should be the same size, the font size should be consitent regardless of text amount, and include an indicator that makes it clear that the anchor text on a numeric rating scale (NRS) refers to the ends of the scale.

When using a verbal rating scale (VRS) on an IVR system, the response choice should be stated prior to the entry value and the cognitive load on the subject having to remember the item and the response scale should be considered. A visual analog scale (VAS) is not suitable for IVR due to its visual nature. If using a NRS on an IVR platform, ensure system is able to capture the maximum number of digits of the response choices, and consider repeating and confirming responses to ensure high quality data.

Conclusion: The assessment of PROs is an increasingly important means of evaluating the efficacy of new medical products. PRO measures should be used when assessing concepts best known by the patient or best measured from the patient's perspective. Advances in technology have substantially expanded the data collection options for clinical trials. The movement from paper-based to electronic PRO data collection has enhanced the integrity and accuracy

of clinical trial data and is encouraged by regulatory agencies. Hence, optimizing the use and usefulness of PRO measures on a variety of electronic data capture platforms is a worthy goal.

The ePRO Consortium has developed best practice recommendations for the development of new PRO instruments to enable them to be more readily implemented on a variety of electronic data collection platforms. PRO instrument developers should consider these recommendations during the PRO instrument development process to prevent the need for significant modifications when the instrument is being operationalized electronically. In addition, the ePRO Consortium has developed best practice recommendations for the migration of existing PRO instruments to electronic platforms. Overlooking key considerations addressed by the recommendations can lead to avoidable challenges. Following the best practices outlined by the ePRO Consortium in this poster should enable more efficient PRO measure migration/implementation and deployment in clinical trials.

Hence, optimizing the use and usefulness of PRO measures on a variety of electronic data capture platforms is an important goal.

The following individuals collaborated to develop this abstract: Celeste Elash, ERT; Jennifer Ross, ALMAC; Bill Byrom, ICON Clinical Research; Paul O'Donohoe, CRF Health; Mabel Crescioni, Critical Path Institute.

T 49

Establishment of Foreign Adverse Event Reporting System in Korea (KAERS-foreign)

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Keywords: Empirica Signal and Topics, ICH E2B(R3) guideline, Individual Case Safety Reports, Korea Adverse Event Reporting System–foreign, Serious Adverse Drug Reactions (SADR)

Method: From 21 August 2014, the KAERS-foreign has received Individual Case Safety Reports (ICSRs) based on ICH E2B(R2) guidelines defining data elements for transmission of ICSRs. For efficiently detecting and managing of Signals, an Oracle Health Sciences safety solution, Empirica SignalTM, was adopted.

Objective: The Korea Adverse Event Reporting System–foreign (KAERS-foreign) was established in August 2014 to collect foreign Adverse Events, especially Serious Adverse Drug Reactions (SADR) with revision of related rules. This study is aimed at introducing the Foreign Adverse Event Reporting System in Korea.

Result: The total number of foreign ICSRs reported from 21 August 2014 to 31 December 2015 was approximately 1.29 million. Of those ICSRs, SADRs were 99.2%. We constructed a dataset for signal detection which was included usable ICSRs through Validation and Data cleansing process. Validation and Data cleansing process includes combining initial and follow-up reports into one final report, identifying drug names provided by WHO Drug dictionaries, and taking the MedDRA terms as standard events terms. Highlighting the limitations of traditional methods such as individual case review, today's drug safety environment calls for strategies to proactively identify and expeditiously manage safety issues. For this reason, Korea Institute of Drug Safety & Risk Management (KIDS) adopted Empirica SignalTM that efficiently provides a pharmacovigilance and safety risk management environment. We are especially going to use data mining technology from Empirica SignalTM to detect Signals and a workflow for classifying and documenting the outputs of earlier reviews and Signal scores provided by TopicsTM.

Conclusion: With the establishment of the KAERS and KAERS-foreign for collecting ICSRs and introduction of Empirica SignalTM for analysis, KIDS established the post-marketing surveillance process periodically providing safety information to Ministry of Food and Drug Safety (MFDS) for supporting evidence-based decision of regulatory actions. Now, KIDS are making a plan to combine domestic and foreign data in one database. Expanding the availability ADR reports by using domestic and foreign ICSRs, production of more meaningful safety information will be possible. Following the global trend, the transition from ICH E2B(R2) to ICH E2B(R3), a revised Guideline released in May 2005, KIDS are also planning to establish a domestic and foreign combination system based on E2B(R3). To prepare for the development a new system, further understanding of the benefits and challenges of implementing E2B(R3) in KAERS is also needed.

T 50

US Trends in Drug Pricing Policy: Past, Present and Future

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Keywords: Drug pricing

Method: This study was conducted primarily via a literature review. The following were included: original and current drug pricing policies in the US, drug pricing policies in other countries that have influenced the US, and unsuccessful policies that have since been withdrawn or amended.

Objective: To evaluate and compare past and present US drug pricing policies and determine the feasibility of pending policies aimed at reducing medication costs for patients and health coverage plans.

Result: Drug prices have increased dramatically due to a higher arbitrary value placed on innovation and limited government regulation. The future of drug pricing policy will depend on several factors including: the US economy, the ability of third-party payers to incur the surge in drug costs, and the 2016 general election.

Conclusion: While the issue of rising drug prices has gained national media attention in the form of public legal action, citizen protests, and presidential candidates- drug pricing policy reform will be unlikely due to several complex factors.

T 51

A Comparison of CDRH Review Times of Original PMA Applications for Products Classified as Combination versus Non-Combination

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Keywords: CDRH, combination products, FDA, MDUFA, medical devices, PMA, review time

Method: The data collected for this study was from publicly available information. Sources used included the FDA's PMA database as well as the FDA's compiled list of approved devices by year.

Objective: The objective of this study is to determine if there is a difference in review time and predictability of the CDRH review of combination products versus non-combination products.

Result: Average review time for combination and non-combination products was sorted by each submission fiscal year (FY) and analyzed based on data collected from original PMAs approved between 2011 and 2015. Product outliers with atypically extensive review times were removed from the data sets along with FYs without any combination product submissions (2005 – 2008 FY) as no correlations could be made. Although a downward trend in review time was observed between 2009 and 2011 FYs for combination and non-combination products, combination products took on average ˜109 days longer to review in 2009 (1001 days for combination products versus 892 days for non-combination products). In 2012 FY, average review time for combination products sharply increased relative to non-combination products with ˜999 days and ˜375 days respectively (624 day difference). Despite a slight increase in the average review time of non-combination products in 2013 FY, the review time for these products continued to trend downward between 2013 and 2015 FYs, unlike combination products that illustrated no consistent trend. Upon further analysis of the variability of the overall data between 2009 and 2015 FYs, greater variation in average review time was established for combination products (SD 449.61) in comparison to non-combination products (SD 320.82).

One noteworthy limitation of the study includes the limited number of combination products studied. Since only original PMAs approved between 2011 and 2015 were reviewed, there were a number of products submitted during the 2009 to 2015 FYs that were not incorporated into the data.
*FY=fiscal year (e.g. 2015 FY=October 1st 2014 – September 30th 2015)
*SD=standard deviation

Conclusion: The trending decrease in review time of original PMA approvals for non-combination products can partly be explained by the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2015. FDASIA reauthorized the Medical Device User Fee Act of 2012 (MDUFA III) that took effect on October 1, 2012. The intent of MDUFA III was to increase the user fees collected by FDA in order to decrease the review time of products reviewed by Center of Devices and Radiological Health (CDRH). This legislation authorized FDA to collect $595 million in User Fees over five years leading to an additional 200 FTEs in CDRH. The commitment letter provided several process improvements for PMA review, including an improved pre-submission process, submission acceptance criteria, interactive review and guidance document development.

Meanwhile, the unpredictability of combination product review as demonstrated by the larger standard deviation compared to non-combination products as well as the non-linear average review time by submission FY, can be attributed to MDUFA shortcomings. In MDUFA III, no additional goals were added specifically for combination products, only an analysis of the impact of combination products on the review process was added. Moreover, the cross-center review of combination products is complicated and the process is not clearly defined. Based upon this data, it can be concluded that by adding combination product-specific goals in the next MDUFA authorization, average review time of combination products will likely decrease and action dates will become more predictable.

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T 52
Evaluating the Level of Medical Information Provided for Health Care Professionals on Consumer Care Websites

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Keywords: Consumer care, medical information

Method: A medical information review was conducted to assess information provided for healthcare professionals on consumer websites for RX-to-OTC switch products. An information rating system was created to direct the evaluation process. A descriptive and numerical analysis of the data will be reported.

Objective: The objective of this study is to rate the level of medical information publically available to healthcare professionals on consumer care websites in order to better assess the type of information provided and gauge consistency within the industry.

Result: The medical information rating system was created to rate consumer websites for availability of a health care professional (HCP) section, availability of product efficacy data, availability of dosing charts, availability of patient teaching tools, and availability of the drug facts label. Topline results showed that of the 27 products rated, only 22% scored above a 2 on the 5 point medication information rating system. Additionally, only 16% of the product consumer sites had a dedicated HCP section. Two therapeutic areas were consistent among products and had the most medical information: cough /cold and analgesics. Both these areas had 74% of products scoring above a 3 on the 5 point medication information rating system.

Conclusion: This study showed that there is an extreme paucity of medical information available for healthcare professionals (HCP's) within the consumer care space and there is generally no industry standard for consistency. A majority of the information found on these websites served more of a marketing purpose than a medical one. It is understandable that the information would be geared more towards a consumer than a HCP, however it was hypothesized that since the products reviewed were once prescription, there would be more medical information available for HCP's. This was not observed since less than 20% of the websites even had a dedicated HCP section. It would be beneficial to add product efficacy data, patient education tools as well as the drug facts label to consumer websites in order for HCP's to make the most educated decision before recommending over the counter products to consumers.

T 53
Calling All Patients: Using a Clinical Call Center to Perform Disease Activity Assessments to Support Treating RA to Target

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Keywords: Call center, disease activity, quality measure, rheumatoid arthritis, satisfaction, treat-to-target

Method: The RAPID3 Pilot was a study of patients with RA in the US that launched in March 2014. Participants were trained on and instructed to complete the RAPID3 every 3 months for the 12-month study. Additionally, in-depth phone interviews were conducted with a random sample of participants.

Objective: The study objectives were to determine 1) if a clinical call center staff could teach patients how to measure their RA disease activity using the RAPID3 and track patient scores over time, and 2) whether patient use of RAPID3 increases patient satisfaction and improves patient-provider dialog.

Result: A total of 152 participants were enrolled in the study and completed the baseline assessment. The mean (SD) age of enrolled participants was 58.7 (11.5) years. The sample population was mostly female (80.9%), White (84.2%), and had post-secondary education (66.5%). The mean (SD) time since RA diagnosis was 14.8 (12.3) years.

More participants (62.5%) elected to complete their follow-up assessments via telephone versus online (37.5%). The number of participants completing follow-up assessments at the 3, 6, 9, and 12 months timepoints were 113, 95, 92, and 88, respectively.

The percentage of participants who were able to correctly calculate their RAPID3 scores was 82.2% at baseline. This percentage increased to 92.9% at the 3-month assessment and to 93.1% at the 12-month assessment.

On a scale of 0 (completely dissatisfied) to 10 (completely satisfied), approximately three-quarters of participants provided a rating of =7 for their overall satisfaction with the RAPID3 as a way of assessing and monitoring the impact of their RA (range: 77.1% to 88.6%). Satisfaction increased with study duration.

Participants reported that discussions with their doctor during their last medical visit was either unchanged (range: 30.6% to 38.7%) or improved (range: 61.3% to 69.4%) compared to medical visits before they began using the RAPID3 questionnaire. No participants reported that discussions with their doctor had worsened.

Conclusion: To our knowledge this is the first study to implement the RAPID3 in a commercial arena with direct outreach to patients. Additionally, this the first study to assess the impact of the RAPID3 on patient satisfaction as well the impact of the RAPID3 on patient dialog with their HCPs.
Most participants were able to successfully complete and score the RAPID3 on their own using the instruction materials provided; however, some participants required some additional support from the study nurse, particularly during the first assessment. There were no significant differences in sociodemographic characteristics between participants who required assistance scoring the RAPID3 and those who did not.

Although 132 participants remained enrolled in the study, only 88 participants completed the final 12-month assessment. Of those lost to follow-up (N=44), most participants were those who completed their assessments online (N=32; 72.7%).

General feedback from study participants about the RAPID3 and the pilot program was positive. The RAPID3 questionnaire was recognized by participants as a useful tool to help track and manage their disease activity as well as encourage discussions with their HCPs. Participants found the RAPID3 easy to complete and were satisfied with its ability to help them understand and take steps towards improving quality of life as a result of their RA. Moreover, patients were in favor of continuing with the program and believed that more patients with RA should be trained on the RAPID3 based on their experience with the tool.

Overall, the RAPID3 Pilot demonstrated that a call center staff is able to successfully teach patients to complete and use the RAPID3 to evaluate their RA disease activity. Operational considerations from this pilot study may prove informative for future initiatives to increase patient engagement and implement a treat-to-target approach for RA.

W 01

Clinical Development in Regulated and Unregulated Markets: Understanding Safety Reporting Requirements

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Keywords: Clinical safety, clinical trials in Asia, pharmacovigilance, post-trial benefits

Method: A review of the regulatory and clinical trial PV systems literature was done. A comprehensive assessment of the safety reporting requirements in China, Japan, Korea, Taiwan, Singapore and some of the other countries in Asia was done to understand the differences and similarities amongst them.

Objective: The objective of the study was to understand the important differences in pharmacovigilance regulations for clinical trials in Asia and other developing countries, compare these regulatory environments to those in the US and EU, and explore measures to manage complexities.

Result: While the West has witnessed major developments in pharmacovigilance, not much has been observed in Asian countries. The study revealed that there is considerable heterogeneity and diversity in the regulatory requirements of the participating countries and a precise knowledge is necessary to streamline pharmacovigilance operations. To exemplify, a local representative is quintessential in China, Japan, and Taiwan, while that is not the case in some of the other countries. Further, the translation of SUSARs to the local language is obligatory in some countries such Japan and South Korea; however, English version is still acceptable in many others. Differences also exist in the mode of submission of reports with different countries opting for manual submission/in person submission or electronic submission. The variations are not limited to the above mentioned examples but extend across many other nuances in the modus operandi of pharmacovigilance.

Conclusion: Asia is the fastest growing pharmaceutical market in the world, providing substantial opportunities for drug development and marketing. Pharmacovigilance being a very sensitive issue demands a high degree of regulatory expertise especially in Global clinical trials. Harmonizing pharmacovigilance regulations in clinical trials has been a continuous challenge due to diverse geographical, cultural and clinical practices in this region. However, with more R&D activities conducted in Asia, there is an important requirement to streamline pharmacovigilance processes. Extensive knowledge of the modus operandi of ethics committees plays a crucial role in achieving the highest standards in patient safety.

W 02

End-to-End Change Control: An Integral Approach to Product Changes, Submissions, and Variation Management

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Keywords: Batch release, change control, CMC, good manufacturing practices, IDMP, information technology, labeling, product information, quality control, regulatory submissions, safety, variation management, variation tracking

Method: According to the EU Guideline Annex 16, as well as 21 CFR 211, the MAH has the responsibility to ensure that a particular batch has been manufactured in accordance with its marketing authorization.
However, the current procedural and technology landscape, to manage product changes from initialization, via regulatory approval, and up to release of the updated product into the supply chain, is very fragmented, as well as being decoupled and functionally compartmentalized.
Although historically explainable, this traditional way of working is very time consuming, inefficient, and leaves a lot of room for error, miscommunication, and associated rework; sometimes even leading to unnecessary recalls.

Having full visibility over changes and associated approvals, pending or approved, across all markets; and providing full control over products released into those same markets is key to making many recalls something of the past.

Now with the introduction of standardized product information, i.e. IDMP, and associated newly formed, or to be formed, technologies, industry as well as agencies can start their transitions to more robust and transparent processes to manage and control the flow of product information and associated product changes end-to-end.
Implementing these concepts will not happen overnight, but the business case is there so, maybe, it is time for planting the seeds and to discuss, conceptually, how this could work.

Objective: 1. To explain the basic concepts of End-to-End Change Control; 2. To provide insights into some of the key benefits and challenges relating to End-to-End Change Control.

W 04

A Value-Driven Decision Making for Drug Development Strategy

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Keywords: Expected net present value, probability of success, quantitative decision making, statistical simulations

Method: Patel et al. (2013) proposed the value-driven framework to optimize sample sizes and trial schedules for Phase III. I propose to optimize the whole development program in one compound by minimizing the risk and maximizing the eNPV from much more macro viewpoint.

Objective: I focus on optimizing the drug development program by quantitative trade-off analysis. We show how to choose the good strategy (e.g. one indication first vs. multiple indications at a time) and to optimize the study designs at each phase to maximize the expected net present value (eNPV).

Result: I presented a method to compute the value of different scenarios while considering the uncertainty into the parameters of drug development based on the various scenario simulations.
Best scenario was selected based on the estimated PoS (probability of success) and eNPV. Simulation results showed that the good strategy has changed depending on the settings of success probability, cost, and net present value for a new compound in our simulation. The sensitivity analyses clarified which factors have impact on the eNPV in each setting. I developed the cumulative function of eNPV for each scenario with PoS and it was very useful to see the operating characteristics of each strategy option.

Conclusion: In order to optimize the productivity of drug development in a pharmaceutical company, it is critical to consider various options of development program and evaluate the value of each strategy quantitatively. Statistical scenario simulation is a good approach to solve the complex multi-dimensional trade-off problems without any human cognitive bias of decision makers. The scenario simulations judged the aggressive strategy (e.g. develop multiple indications at a time) was better than standard plan (e.g. develop unique indication first) in some settings. It was a seemingly counterintuitive result and therefore I found that such a quantitative analysis is critical to support the good decision making. I concluded that a quantitative decision making approach that is available from various scenario simulations is critical by maximizing eNPV and minimizing risk at each drug development phase.

W 05

Unusual Data Pattern Analysis in a Large Pharmaceutical Company

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Keywords: Centralized monitoring, data integrity, misconduct, risk-based monitoring, statistical monitoring

Method: SAS JMP Clinical was used to search for unusual data patterns in clinical trial data in Novo Nordisk. Standards for further data drilling and visual outputs were created and the anchoring in the organisation focused on building collaboration with different professional disciplines.

Objective: We aim to summarize the lessons learned from the practical implementation of unusual data pattern detection in clinical trials, the process of analysis and the communication of observations to different stakeholders.

Result: A unit with two full-time analysts with a background in trial conduct was established. During 2015 the analysts analysed 18 trials with the aim of identifying unusual data patterns that could jeopardize the integrity of trial data. A standard set of analyses and visual statistical outputs were applied across trials independent of trial teams and trial design. Subsequently, the analyst supported the trial teams in interpreting the outputs to avoid interpretation errors due to noise or false-positive findings. The conclusions from the unusual data pattern analyses led to decisions and actions handled through existing procedures. To facilitate interpretation and decision making an algorithm was created accounting for the timing of unusual data pattern analyses e.g. during or after trial conduct. The timing of analysis potentially affected decisions and who to involve in decision making. The algorithm included an overview of possible actions to guide the trial teams. Initially, the trial teams were themselves accountable for creating appropriate documentation of any observations.

As experience was gathered, the analyses became better adapted to the specific trial designs and their potential risks. Thus, the unusual data pattern analysis now assumes a more appropriate combination of statistical outputs and graphics tailored to trial risk and therapeutic area. Furthermore, a process for how to document the analysis performed, observations found and actions taken is being implemented across trial teams to facilitate a uniform documentation practice.

Conclusion: Due to data complexity, multivariate dimensionality and noise the standard JMP Clinical output are not immediately understood by the diverse professional disciplines involved in trial conduct. The outputs from the analysis and further data drilling exercises therefore needs interpretation and simplification before being presented to trial teams. A framework of standard analyses and subsequent standard output is necessary. Additionally, the analyst should serve in a guiding role in the discussion of the significance and relevance of the statistical findings to avoid biases especially in terms of false-positives or non-important observations.

In conclusion, a simple and transparent process is essential. This should build on an interdisciplinary model where the standard statistical output and in-depth data drilling is supplemented with an evaluation process involving diverse disciplines within trial conduct. With this setup, the analyst assumes leadership of the process and sets standards to establish a coherent collaborative approach and to translate findings into decisions and actions manageable by the trial teams.

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W 06

Design of Physicochemical Compatibility Studies for Sterile Injectable Products: Key Lessons from Recent Filings

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Keywords: Compatibility studies, in-use stability studies, microbial challenge, sterile injectable products

Method: The presentation provides an overview of recent experience related to pharmaceutical development and regulatory approval of in-use stability (compatibility) studies in support of global marketing applications for sterile injectable products. Two detailed case studies are presented on lyophilized sterile drug products for reconstitution and dilution: one including a product that has limited solution stability, and the other including a product with a long administration (infusion) time. The presentation explores the different approaches and unique challenges associated with the specific product types and regional regulatory requirements.

Objective: Describe global regulatory requirements and key considerations for the design of in-use stability (compatibility) studies for sterile injectable products. Formulate and deploy an appropriate scientific and regulatory strategy for compatibility studies depending on product specifics to ensure expedient global regulatory approvals.

Result: For Product A (product with a limited solution stability), in-use stability studies were conducted to support 2 separate indications with different required infusion times. In-use storage conditions were proposed for immediate and delayed drug product administration. Following the initial submission of global marketing applications, the originally proposed in-use storage conditions were revised based on the feedback received from the FDA and EMA to ensure that the administered drug product complies with its specifications up to point of administration while minimizing the drug product degradation. A strategy to align the legacy global filings was developed and successfully deployed.

For Product B (unpreserved product with a long administration time), in-use stability data to demonstrate acceptable chemical and physical stability for up to 30 hours and acceptable microbial stability over 60 hours was provided in the original NDA. Based on the guidance received from the FDA regarding the design of post penetration stability studies for sterile drug products, additional in-use stability studies with spiked microorganisms were conducted. These studies supported a hold time of up to 8 hours at room temperature, which was not sufficient to enable the required infusion time of 24 hours. Further studies were performed with lower starting inoculum levels and using either a bacteriostatic agent or an in-line sterilization filter. The results of the study with a bacteriostatic agent demonstrated that this approach was not feasible, as the allowable daily intake of a bacteriostatic agent was exceeded while still failing to reach the required minimal inhibitory concentration. On the other hand, microbial challenge studies with in-line filters demonstrated the effectiveness of microbial removal and provided a viable solution to ensure the control over adventitious pathogens that may be introduced during solution preparation.

Conclusion: It is important to study the physical, chemical and microbial properties of the drug product that are susceptible to change during storage over the period of the proposed in-use shelf-life. Lyophilized sterile drug products for reconstitution and dilution may present special challenges due to limited solution stability or long required infusion times. For the case of a product with limited solution stability, degradation kinetics after reconstitution and dilution was thoroughly understood and suitable in-use storage conditions developed to ascertain that the product complies with its specifications up to the point of administration to the patient. The proposed in-use storage conditions also took into account the typical drug product preparation, handling, and transportation times from hospital pharmacy to the patient. For the case of a product with a long administration time, the risk of contamination with adventitious pathogens that may be introduced during solution preparation was addressed. Microbial spiking studies have demonstrated that the diluted drug product supported microbial growth over the proposed storage time. Thus, two risk mitigation approaches were proposed and examined: use of a bacteriostatic agent or an in-line sterilization filter. The latter approach was shown to be the commercially viable approach that was approved by the FDA.

W 07

Effectively Evaluating Risk Minimization: Mitigating the Risk of Inadequate Assessments

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Keywords: Assessment, effectiveness evaluation, REMS, risk minimisation, risk mitigation, RMP

Method: This review analyzed EU assessments of risk minimization effectiveness: a) conducted by Pope Woodhead that are complete or have started data collection; and b) conducted by other organizations that have publically-available results identified through a literature search.

Objective: To review studies conducted to evaluate the effectiveness of additional risk minimization (RM) measures in the EU.

Result: Effectiveness evaluation of additional risk minimization has been mandatory in the EU since 2012. Good Pharmacovigilance Practices (GVP) Module XVI was released in March 2014 and includes guidance on evaluation. The results of some evaluations performed under this new environment have now become available. This review of available assessments indicates significant challenges in the design and implementation of evaluation studies across EU countries. Key challenges identified included:

- Developing better-quality instruments for evaluation
- Collecting appropriate data that have value
- Navigating specific requirements of individual eu countries
- Assessing outcomes of rm programs
- Selecting suitable evaluation populations to reduce bias
- Gaining sufficient participation due to the perceived burden of performing evaluations
- The lack of baseline, comparators (tool users vs. Non-users) and benchmarking
- Interpreting and acting on evaluation results

Conclusion: Additional RM measures may be required for a drug to ensure patient safety and a positive benefit-risk balance. These are described in the relevant risk management plan, such as an EU-RMP or REMS. They typically include educational tools but may also have more stringent elements to assure safe use. Although this review focused on the EU environment, many of the same factors apply for assessment of REMS. Assessing the effectiveness of risk minimization is currently one of the key challenges within the risk management field. Many of these challenges could be solved through the use of innovative approaches and potential solutions are presented. As risk minimization increasingly switches from paper-based to electronic approaches which reflect the preferences of end-users, opportunities are arising for interactive web-based RM tools that incorporate real-time effectiveness evaluation.

W 08

Increasing the Efficiency of Investigator-Initiated Research in China

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Keywords: Investigator-initiated research (IIR) management in China

Method: The globally standard policy and process management of IIR in Pfizer was elucidated, and the overall data and study management on China IIR were summarized.

Co-Authors: Qing Gu, Sherry, Zhang, Jiayi Yan, Ning Shao, Chengming Gu, Alexander Kostek

Objective: To understand the globally integrated operational process and tools for IIR management that achieve the maximal effectiveness, compliance and deliverables, and gain an understanding of the IIR process in China and its unique challenges.

Result: IIR is a type of Pfizer non-sponsored study, which enables investigators around the world to have the opportunity to design and conduct their study, foster innovation in medical research, and provide more valuable data to better understand drug development and disease therapy. All IIR in Pfizer must adhere to Global Standard Operating Procedure (GSOP) and Work Instruction (WI). The unique Integrated System for Pfizer Investigator Initiated Research (INSPIIRE) is utilized throughout the entire study process from submission to close. The audits make sure IIR are aligned with SOP, WI, local regulation and compliance.
In the past 10 years, there have been nearly 400 IIR studies submitted and conducted by investigators in China, including about 240 standard IIR and 150 more CG in various therapeutic areas: cardiovascular, anti-infectives, oncology, inflammation, urology, etc. Among them, 84% are in clinical research and 16% are in pre-clinical research. Of the clinical research, 61% is interventional study and 39% is non-interventional study. The grant review committee conducts a meeting monthly by therapeutic area. The study status and issues are reported to all stakeholders monthly. For each issue, the IIR team and medical advisor communicate with investigators and follow up to make sure it aligns with protocol and contract. Up to now, over 100 IIR studies in China have published the results in peer reviewed medical journal or conferences, which is a good measure of the study quality and shows that the studies provide valuable data which have impact around the world. Furthermore, to ensure better alignment with SOP and WIs, the monthly quality control by sampling is conducted and the issues are resolved promptly. We credit this for our good 2015 audit results in China IIR.

Conclusion: Highly efficient IIR management is based on the globally integrated SOP and tools, good communication internally and externally, and a good quality control process.

W 10

Process and Pitfalls of Preparing Breakthrough Therapy Designation Documents

Robin Whitsell
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Keywords: Best practices, breakthrough therapy designation, regulatory medical writing, strategy, submissions

Method: Whitsell Innovations, Inc. (WI) has examined our processes for writing BTD submissions to FDA since the 2012 inception of this designation. This poster will: detail BTD requirements, map best-practice processes, recommend strategies for success, and identify potential pitfalls in team engagement.

Authors: Lisa Vadola, PhD; Karry Smith, PhD, MPH; Kelly Kilibarda, PhD; Monique Pond, PhD; Ann Winter-Vann, PhD; Natalie Herr, PhD; Robin Whitsell, BA, BPh

Objective: We will detail the Food and Drug Administration (FDA) submission process for Breakthrough Therapy Designation (BTD) documentation, highlighting strategies for efficiency and discussing potential pitfalls.

Result: Thirty years ago, Congress introduced the Orphan Drug Act to provide incentives for the pharmaceutical industry to pursue drug development programs for rare medical conditions. However, this act did not address the long cycle times required for FDA review, prompting the creation of expedited review programs. Introduced in 2012, the BTD provides drug sponsors with opportunities to shorten both their investigational new drug (IND) application review time and their overall development time, potentially leading to significantly faster availability to patients. Submission of a request for BTD can occur

concurrently with the IND or afterwards, but ideally no later than the end-of-Phase 2 meeting. Per the FDA's website, the formal request for BTD must include a cover letter, information about the drug or biologic, the basis for considering the drug to be intended to treat a serious condition, and preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies. The submission of this request involves careful coordination between the Sponsor, medical writers, and other study personnel. We have created a process map and a strategy sheet to aid the medical writer in performing an information gap analysis at the initiation of authoring, managing the authoring and review of the document, and coordinating handoff to publishing and submission functions.

Conclusion: Using the strategy sheet and guidelines WI has provided will allow for efficient submission of the formal Request for Breakthrough Therapy Designation documentation.

W 11

Integral Authoring: A New Paradigm for Data-Driven Structured Authoring of Documents in the Life Sciences Industry

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Keywords: Country specific submission, global dossier, IDMP, integral system, labelling, master data, MDM, regulatory Information, regulatory programm, variation

Method: The poster will utilize the example of labeling documents to discuss the potential options for automation of business processes, and business intelligence driven decision making, using the Integral reflection of MDM- and RIM-driven business processes.

Objective: Regulatory Information Management (RIM) in broader context has been challenged by permanent Health Authorities (HA's) driven changes like IDMP or eCTD module 1. RIM can also become part of MDM itself.

Result: The traditional approach to managing data and content separately has been driving the modularity of respective focused applications in the Life Sciences industry. Those applications, developed to support specific parts of a process, were built proprietary, with a simplified data model and needed to be interfaced with each other to attempt to support the end to end process. Both aspects led to increasing complexity and exponential maintenance efforts of such systems and interfaces. Regulatory Information Management (RIM) including submission, document, process and data management has been challenged by permanent changes in regulatory standards resulting in higher standards for the delivery of consistent data and content to Health Authorities (HA's). One timely example of this is the recent ISO IDMP/XEVMPD or eCTD Module 1 requirements. On one hand, proper Regulatory Information (RI) relies on proper Master Data (MD). On the other hand, RI can also become part of MD itself. The question arises, what boundaries and synergies can be identified and utilized? What setups would allow mutual leveraging in order to positively impact business process designs to increase and sustain a company's competitiveness and efficiency?

Conclusion: The use of an Integral design model within solutions for managing content, processes and data, enables an entity (object) oriented approach; processes and data can therefore be managed within the same entity model. In this context, structured authoring becomes a natural element of the overall capability as data entities can drive automation of content entities and in this way ensure their consistency.

W 12

Tipping Point Sensitivity Analysis in Continuous Asthma Quality of Life Questionnaire Endpoint

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Keywords: Asthma, missing data, quality of life, tipping point analysis

Method: Sensitivity analysis using the tipping-point approach will be used to assess the robustness of the primary analysis approach. The Variant 3 of the tipping point as described in Ratitch et al. (2013) will be applied.

Objective: In this paper, sensitivity analysis will be performed using tipping point approach; based on recent FDA requests in current respiratory trials. Analysis will present randomized clinical trial questionnaire data.

Result: Clinical Trial data illustrates sensitivity analysis in multiple imputations under the MNAR assumption by searching for a tipping point that reverses the study conclusion. The Variant 3 of the tipping point as described in Ratitch et al. (2013) will be applied. In that approach, missing data are first imputed for all visits under the MAR assumption, and then the worsening/shift is applied. This is repeated until the result is no longer statistically significant. The results of the sensitivity analysis indicate that the tipping point approach is not intended for the primary analysis method and is only used for the sensitivity analysis and the results are robust as compared to primary analysis. Details of numerical results will be provided in the poster.

Conclusion: One method, tipping point approach, has gained the popularity recently as an approach for performing the sensitivity analysis under the missing at not random (MNAR) assumption. In other words, the tipping point approach is like a progressive stress-testing to assess how severe departures from missing at random (MAR) must be in order to overturn conclusions from the primary analysis. The value of tipping point may be compared to the clinical meaningful difference or the estimated treatment difference from the primary analysis. This may provide a sense for us to interpret the robustness of the analysis results against the handling of missing data.

W 13

Switching Endpoints Based on an Interim Analysis

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Keywords: Adaptive design; interim analysis

Method: This is development of methodology to use a secondary endpoint from an interim analysis as the primary endpoint for the final analysis.

Objective: Based on the results of the interim analysis, it may be decided to switch the roles of the primary endpoint and one of the secondary endpoints for the final analysis at completion of the trial.

Result: The level of the test at the conclusion of the trial must be adjusted to control the overall Type 1 error rate. The adjustment incorporates both the interim analysis and

the change in the primary endpoint, and is determined from the correlation between the two variables and the sample sizes for the interim analysis and the final analysis. Thus the adjustment can also be useful for re-estimation of the sample size for the end of the study, if necessary.

Conclusion: A secondary endpoint may become the primary endpoint, as long as the decision is made by an unblinded committee and the level of the test is adjusted appropriately.

W 14

Evaluating REMS Burden: A Comparative Time Analysis of Three Options for REMS Stakeholders to Perform Mandatory REMS Tasks

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Keywords: Celgene REMS, ETASU, REMS, REMS burden, REMS tasks, risk evaluation mitigation strategies

Method: We performed a simulated comparative time analysis of REMS stakeholders completing mandatory REMS tasks across 3 different options/channels (online, telephone interactions with Celgene Customer Care Representatives (CCR), or Interactive Voice Recordings Systems (IVR)).

Objective: Describe time differences among 3 available options/channels (online, telephone w/CCR, or IVR) for REMS stakeholders to perform mandatory REMS tasks (enrollment, survey participation, pharmacy dispense confirmation) for the Celgene REMS programs for thalidomide, lenalidomide, and pomalidomide.

Result: Due to the safety risks of embryo-fetal toxicity associated with thalidomide, lenalidomide, and pomalidomide, each product is available in the US only through a Risk Evaluation and Mitigation Strategy (REMS) program. The Celgene REMS programs require prescribers, patients, and pharmacists to complete mandatory REMS tasks beyond typical prescription/dispense interactions before those products can be taken by patients.

The objective was to analyze the time it takes for a REMS stakeholder to perform the same REMS task across the available options/channels. Five Celgene representatives executed a total of 110 tests representing 5 different REMS tasks (prescriber enrollment, patient enrollment, prescriber survey participation, patient survey participation, and pharmacy dispense confirmation) across multiple channels. Associated execution times were recorded. It was assumed that the times were representative of the REMS stakeholder population. The execution times for the same REMS task across channels varied substantially. For a new Adult Male patient enrollment task, the average execution time using the prescriber/patient online portal (www.CelgeneRiskManagement.com) was 6.7 minutes (285% faster) compared to 25.9 minutes with a CCR ($p<2.2 \times 10\text{-}16$). To enroll a new prescriber using the online system, the average time was 1.3 minutes, while with a CCR averaged 21.9 minutes ($p<2.2 \times 10\text{-}16$). To complete the prescriber survey task, the average time to complete 3 prescriber surveys using the online system was 3.1 minutes, 4.9 minutes with a CCR, and 10.7 minutes using the IVR. The average time to complete a patient survey online was 1.3 minutes, 1.8 minutes with a CCR, and 4 minutes using the IVR. For a pharmacy dispense task, the average of 5 dispenses using the online Pharmacy Portal (www.CelgeneREMSPharmacyPortal.com) was 95% faster than CCR ($p= 5.05 \times 10\text{-}7$). The averages for Pharmacy Portal, CCR and IVR were 1.7 minutes, 3.4 minutes, and 11.3 minutes respectively.

Conclusion: In this comparative analysis, the performance of REMS tasks using available online systems was significantly faster than other available options/channels to perform the same REMS tasks, while the IVR required the most amount of time. The perception of REMS burden may be driven by the experience stakeholders have when interacting with REMS programs, their understanding of REMS program rationale to mitigate serious safety risks, and treatment outcomes. We acknowledge that stakeholder preference will determine how they perform REMS tasks and how they interact with REMS programs. Ultimately, REMS burden on stakeholders is determined by multiple factors in addition to time spent on mandatory REMS tasks. We propose, however, that more education and awareness of available efficient options to complete REMS tasks be provided to REMS stakeholders to facilitate the decrease of REMS burden. Finally, we recommend that prescribers, patients, and pharmacy stakeholders of the Celgene REMS programs consider, if and when possible, utilizing online systems to complete their Celgene REMS transactions to potentially lessen some of the REMS burden by reducing the time it takes to complete these mandatory REMS tasks.

W 15

Applications of Expanded Access/ Compassionate Use Programs for Evidence Generation

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Keywords: Evidence generation, expanded access programs, treatment patterns and effectiveness, value messages

Method: Key attributes to the design and conduct of chart review studies in expanded access populations will be described including: streamlined site identification and enrollment and focused data collection and endpoints that can be addressed and disseminated.

Objective: Understand what evidence and value messages can be generated from chart review studies in expanded access patient populations and describe best practices for collecting data from these programs to inform real-world use, treatment effectiveness and clinical outcomes.

Result: Expanded access programs, also known as compassionate use and named patient programs provide peri-approval drug access to patients with limited available treatment options based on voluntary physician requests. These programs are conducted prior to market approval and offer an opportunity to understand the impact of investigational medications in a non-trial setting. While patients provide informed consent and are enrolled into these programs, these programs typically do not involve data collection beyond safety data (serious adverse event, adverse event of special interest). There is a wealth of information that can be gleaned from these programs and data collection would be the first evidence of how the drug is performing outside of the highly controlled clinical trial setting. Peri-approval chart review studies of patients in expanded access programs offer an important opportunity to inform clinical, health economic, and market access decisions by: characterizing patterns of use and associated treatment costs and understanding the clinical impact of investigational medications in a non-trial setting. Data on confounding variables

possibly excluded in trials and outcomes from sicker populations can be evaluated.

Conclusion: With the increase in expanded access programs and the need to understand drug performance outside of clinical trials, chart review studies can be successfully undertaken to inform on early drug use in non-trial settings with respect to patient characteristics, treatment effectiveness and drug safety profile.

W 16

An Investigation Into the Distribution of BRCA 1/2 Mutation/Ness Breast and Ovarian Cancer Populations

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Keywords: BRCA 1/2, breast cancer, global feasibility, Incidence, ovarian cancer, prevalence

Method: For this study, we reviewed literature and databases from existing investigations that include BRCA1/2 ovarian and breast cancer mutation prevalence, comparing the methods and results to build an overall picture of BRCAmut distribution.

Objective: The objective of this study is to identify the patient distribution of BRCA1/2 mutation specific Ovarian and Breast cancer populations that could potentially benefit from targeted therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors.

Result: Quantitative data included incidence rate and prevalence for breast cancer and ovarian cancer by country (GLOBOCAN). BRCA 1/2 mutations are shown to range from 5–15% in ovarian cancers and 20–25% in hereditary breast cancers (NIH. 2015, Ramsus S.J et al. 2009). BRCAness or homologous recombination repair deficiency (HRD) tumors show a large degree of complexity as the HRD phenotype can be present in many ovarian breast cancer tumor types; up to 50–60% of women with epithelial ovarian cancer have BRCAness phenotype (Edmondson R.J. 2011). Literature indicates that there are ethnic groups more predisposed to the BRCA 1/2 mutation than others;

'...the frequency varies, geographically and between different ethnic groups.' (Ramsus S.J et al. 2009). Observing different ethnic/ racial population show that these mutations are more common in Ashkenazi Jewish, Norwegian, Dutch, Icelandic, African Americans, Hispanics, Asian Americans and Non- Hispanics white population (NIH. 2015). Data base – WHO GLOBOCAN 2015 -Region level OC and BC patient distribution (Incidence/ Prevalence)

- North America (BC: 91.6, 671236; OC: 8.1, 41587)
- CEE (OC:1.4, 48950; BC: 47.7, 304311)
- Australia/ New Zealand (OC: 7.6, 2954; BC: 85.8, 43931)
- Western Europe (OC: 7.5, 15987; BC: 91.1, 399841)
- Latin America (OC: 536, 32328; BC: 47.2, 354772)
- Africa (OC: 4.8, 27706; BC: 36.2, 291061)

Conclusion: The proportion of patients with breast cancer or ovarian cancer that have the BRCA 1/2 mutation can vary, as shown by reviewing literature.

- Regional distribution between breast and ovarian cancer patients differs greatly with OC having the highest incidence and prevalence within Western Europe compared with breast cancer which has the lowest. As BRCA 1/2 mutation are hereditary this may suggest that there may not be a strong link between the occurrence of breast and/ or ovarian cancer stemming from BRCA 1/2 mutations.
- An increased awareness of the distribution of breast and ovarian cancer patients with the BRCA 1/2 mutation could help future feasibility studies and clinical strategies, to better target effective countries and/ regional areas.
- This investigation has identified the key ethnic groups that predominantly have this mutation.
- Breast cancer screening practices may have an effect on the ranges indicated within this investigation – as some countries class women at high-risk of breast cancer through family history or regular screening with the use of mammograms/ MRI.
- The robustness of the findings were bolstered by combining a range of data sources and types with the additional data from GLOBOCAN, the review of previous investigations into BRCA 1/2 populations and calculation of new patient populations within regional areas.

W 17

Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names

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Keywords: Drug name confusion, medication error, nonproprietary name, proprietary name, wrong drug

Method: We evaluated 224 drug name pairs on ISMP's List of Confused Drug Names. We analyzed the construct of the names to determine which characteristics applied to the name pair and may have contributed to name confusion.

Objective: Provide a descriptive analysis of characteristics that are common among drug name pairs on the Institute of Safe Medication Practices' (ISMP) List of Confused Drug Names.

Result: Of the 224 drug name pairs, 154 (68%) of the drug name pairs shared the same first letter, 118 (52%) contained a shared letter string of at least three letters, and 206 drug name pairs (91%) had a difference in the number of letters by = 2 letters. We also obtained the Phonetic and Orthographic Computer Analysis (POCA) score for each name pair. POCA is an analytic tool designed to help identify drug and biologic names that are phonetically and orthographically similar to one another. The majority of drug name pairs (n=121, 54%) were categorized as moderately similar with a combined POCA score of = 50 to = 69. Ninety-nine percent of the drug name pairs reflected at least one of the following characteristics: the same first letter, or a shared letter string of at least three letters, or similar number of letters.

Conclusion: We found most of drug name pairs started with the same first letter and more than half contained a shared letter string of at least three letters in the prefix of both names. Additionally, we also determined similar lengths of the names are also a major contributing factor in the confusion of these drug names. We also found that 75% of the drug name pairs had a combined POCA score of =50. These important characteristics are key in identification of potentially confusing drug names more efficiently, and should be considered when formulating and evaluating proposed proprietary drug names in order to minimize the risk of look-alike or sound-

alike drug name confusion that can lead to medication errors.

W 18

Quality Consistency Assessment for Botanical Medicines using Chromatographic Fingerprint

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Keywords: Batch consistency, botanical medicines, fingerprint, quality control, statistics

Method: Our work provides a comprehensive review on current statistical models in fingerprints similarity assessment from IND/NDA submissions and literatures for botancial products. We also develop a more sensitive analysis to assess batch consistency.

Objective: To have an overview of the current issues regarding the quality control of botanical products; to understand some bacis statistical methods applied to batch consistency assessment for botanical products.

Result: We will provide a comprehensive review on current statistical models in fingerprints similarity assessment from IND/NDA submissions and literatures. Advantages and disadvantages of each method and potential review issues will be presented. Second, we will study two potential similarity measurements, which are the correlation index and the chi-square type index, to quantitatively evaluate the similarity in fingerprints. In order to adjust for the natural variability within the same products, we also propose to divide the correlation or the chi-square difference by the measure of fingerprints of two reference batches. Such measurements are called ratio of correlations and ratio of chi-squares. Simulation studies to compare our proposed model with existing models will be conducted and discussed. We will also illustrate our model through real-data example. Results of this project can facilitate IND and NDA reviews in quality control of botanical medicines by providing evidence-based method.

Conclusion: The current approaches have their limitations to assure the quality consistency for botanical product. A more advanced approach is needed.

W 19

Implementing and Monitoring the Use of Interactive Risk Communications

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Keywords: Communication,digital, effectiveness, innovative

Method: We are deploying interactive apps that educate HCPs and patients about the appropriate use of a drug requiring sterile preparation and administration at home. The apps collect utilisation and patient knowledge data useful in assessing implementation success and effectiveness of educational content.

Objective: In the EU, GVP XVI requires effectiveness evaluation of risk minimisation measures. As this is difficult to achieve for paper-based communications we are exploring how to better engage users and collect rich effectiveness data through interactive web-based applications.

Result: We deployed web-based educational applications for healthcare professionals and their patients to encourage the appropriate use of a drug. The education is provided in 17 local language variations (34 URLs).

- The HCP focussed tool provides important risk minimisation education related to appropriate preparation and self-administration of the drug at home for patients they believe capable of following instructions. The tool is used during self-education and patient training. To augment the guidance, links to product labelling and downloadable PDF guides are included. HCPs can access the patient version of the tool to demonstrate relevant sections of the resource to patients.
- The Patient apps offer detailed training on the sterile preparation and administration of the drug through short training sections used either for self-education or as stepwise guidance followed when taking the medicine. To augment the educational content, users can download printable materials and answer quizzes covering key safety messages.
- The apps collect anonymised utilisation data from each user every time they are accessed. This data is used to evaluate the effectiveness of the initial deployment, ongoing use and patient knowledge. Data collected includes:
  - Utilisation of each of the country/ language variants to assess the effectiveness of publicising their availability across markets
  - Frequencies of repeat uses and timing data provided by anonymised individuals (e.g. HCPs using the application for training or patients accessing guidance during a self-administration event)
  - Download frequencies or use of links to product labelling to show the value of supplementary data
  - Healthcare professional feedback on the utility of the apps for managing risks
  - Improvements in patient's knowledge with repeated use via quizzes is used as a surrogate for behavioural outcomes

Conclusion: This is the first multi-lingual pan-European web-based risk minimisation platform collecting real-time effectiveness data. The system delivers important advantages over paper-based tools and PASS surveys.

1. They provide a richer end-user experience increasing engagement and likelihood of re-use.
2. Collecting data from all users gives a more representative evaluation of efficacy than via commonly employed surveys. Actual utilisation behaviour rather than stated behaviours from surveys (limited by recall and social desirability biases) is observed.
3. The uptake and use of the materials can be monitored regularly, which is not possible with paper.
4. The status of implementation and value of publicising these apps is easily assessed through monitoring HCP and Patient registrations.
5. Repeat use, sections visited and timing data delivers insights into how tools are used (e.g. initial self-training, HCPs training patients, patient's use during an administration event)
6. HCP feedback helps understand their perspective on app's utility.
7. Download frequencies and access to labelling demonstrates the usefulness of supplementary information.
8. Embedded knowledge tests provide an opportunity to educate patients and measure their understanding of key risk messages within the guidance. Monitoring responses longitudinally, e.g. via repeat knowledge tests, can show evidence of learning.

Monitoring the effectiveness of implementations and the effects of the educational content of these applications

allows pharmaceutical companies to manage risks proactively. Data can help to determine corrective actions needed to improve tool uptake or raise users' knowledge. Feedback from embedded surveys help understand end-users expectations of the educational materials. The wider adoption of these proactive approaches necessitates the development of new capabilities, processes, governance mechanisms and people in order to maximise the patient benefits they can deliver.

W 20

Digital Health Networks as a Change Agent of Public Perceptions for Clinical Trials

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Keywords: Digital health networks, patient engagement, social listening, virtual communities

Method: The study was conducted over a 4-month period (Oct 2015 to Jan 2016) and comprised of web-based research comparing major digital health networks e.g. virtual medical consultation and healthcare e-commerce etc. supplemented by in-depth profiling and analysis of selected platforms.

Objective: This investigation looks at digital health networks in China, examines how they engage with patients, caregivers and physicians and also how social listening on these platforms offers insights that are important to consider when we address key challenges in clinical research.

Result: The study identified more than 60 digital health networks (close to 20 digital health websites and more than 40 healthcare mobile applications) popular in China. The key functions of these networks include virtual medical consultation, web or app-based appointment making to consult with physicians, disease education for patients, sale of pharmaceutical and consumer healthcare products on e-commerce platforms and knowledge sharing amongst physician communities etc. It found that consumption of digital health is largely concentrated on mobile platforms (versus web) – 58% as compared to 42% in China. Conversely, the web-based health network users were more active (more than 150 million users in June 2015) than those accessing digital health networks on mobile devices (30 million users).

A more in-depth analysis of the top 10 web and mobile digital health networks shed light on the following for each of these platforms:

- Target audience
- Primary functions
- Usage traffic
- Value proposition
- Digital health networks were found to be largely providing the following services to users:
  - Productivity applications for medical professionals
  - Health Information System (virtual medical consultation)
  - Appointment making for face-to-face medical consultation and patients record management)
  - Knowledge exchange within physician communities
  - General medical information
  - e-Commerce platforms for online purchase of pharmaceuticals and consumer healthcare products
  - Patient/caregiver education on diseases management and treatment options
  - Patient support forums for sharing of patient journey and treatment experience

As anticipated, the conversations over the digital health networks offered a glimpse into the journey that patients/caregivers go through, their considerations etc. as they seek to find answers about their medical conditions on virtual communities.

Conclusion: Technology and digitization are reshaping lives and minds around the world. Changes in the way information is shared and consumed has resulted in previously unimaginable changes to lifestyles. As the bio-pharmaceutical industry increasingly focuses on involving and engaging with patients in early stages of clinical research, it needs to be more resourceful and think harder for ways to plug into conversations that patients, caregivers and physicians are having for a glimpse of what is keeping them up at night.

In China, an explosion in mobile usage is seeing retail spending on mobile devices grow by over 100% in 2015. The same trend is observed in China's healthcare industry where there has been an unprecedented growth in the number of digital health networks in China. Patients are receiving medical advice from physicians via mobile applications and placing orders for pharmaceutical and consumer healthcare products via e-commerce platforms. Patients are searching for clinical trials recruiting in China on clinicaltrials.gov and are contacting investigators on some of these digital health platforms to understand their eligibility to be consider for trial enrollment.

Digital health networks are set to change the way that dots between the 3Ps (Patients, Physicians and Pharmaceutical companies) are connected. Companies conducting clinical research in China will want to harness the potential of these communities through social listening for a better appreciation of voice of patients. Knowledge of what patients find important will be useful to consider when we address challenges to conducting clinical trials e.g. protocol design, patient recruitment and retention. An understanding of how these virtual communities operate may help companies accurately identify engagement opportunities with key stakeholders across the life-cycle of clinical research and pharmaceutical product development.

W 21

Utilizing Simulations to Enhance Randomization Methodology Decision Making

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Keywords: Block size, minimization, randomization methodology, simulations, stratification, treatment balance

Method: Configurable SAS simulation programs can be readily adapted to individual protocols to explore the design properties (expected treatment balance) for various randomization methods (stratified blocked rand., minimization, etc.) and associated parameters (block size, biased-coin probability, etc.).

Objective: This poster will illustrate, via a case study, how simulations can be an effective tool in evaluating study design decisions by investigating expected treatment balance resulting from different randomization methodologies and associated parameterization.

Result: CASE STUDY: Design: 2,000 randomized subjects, 2:1 treatment allocation ratio, 3 stratification factors Gender (male/female), Disease Severity (high/low), and Age (<=10, >10 or <18, >=18), with/without stratifying by 200 Sites (25 high, 50 medium, 50 medium-low, 75 low enrolling).

Scenario 1: to evaluate expected treatment balance when utilizing a stratified blocked randomization vs. minimization with biased-coin assignment.

Scenario 2: based on a stratified blocked rand. methodology without stratifying by Site, determine the minimum amount of subjects that each site needs to randomize to ensure that at least 1 subject is randomized to each treatment group.

Simulations: 100,000 trial runs for the above scenarios were generated based on real-life assumptions for factor level distributions (including Site) via configurable SAS programs, showing the expected treatment balance (P[Imb<=X (X=0,1,2,3,4,etc)] at Study, Site, and Strata level).

Scenario 1 (Results): simulations demonstrated that the inclusion of Site as a stratification factor based on stratified blocked methodology was not an option due to Study/Factor level treatment balance being compromised. Even when utilizing minimization methodology, Site balance was not sufficiently controlled to justify the loss of treatment balance (power) at the Site/Factor levels.

Scenario 2 (Results): theoretical probabilities were calculated at the Site level for the number of subjects required for both treatment arms being represented; simulations were then utilized to validate the calculated theoretical probabilities based on varying underlying Site distributions. Based on the simulation results, a stratified blocked randomization design based on the 3 factors only (excluding Site) was selected, where Sites were only permitted to participate if guaranteed to be able to enroll the minimum number of subjects with low probability of both treatment groups not being represented at Sites, as identified via the simulations.

Conclusion: Treatment balance for a clinical trial is critical as the resulting drug effectiveness can be difficult to identify if balance is not achieved. Therefore, the various components of the randomization design that can impact treatment balance should be carefully considered upfront at the time the protocol is being drafted. Determining the optimal design for randomization via SAS simulations is an effective way to help identify how best to maintain treatment balance for the study, as shown in the above Case Study. Further, the simulation results of the Case Study illustrated the minimum number of subjects randomized at each site that had at least 1 subject randomized to each treatment arm, which assisted the clinical study team with their site selection.

While this Case Study focused on specific scenarios, simulations can also be used for numerous randomization design decisions such as stratification inclusions, randomization methodology, and various randomization methodology parameters. Additional real life expectations can be incorporated, such as sample distributions, to enhance the accuracy of the treatment balance results. Concerns for enrollment can also be assessed by including drop-out rates, which may help identify the need for replacement randomization. Because of the SAS simulation program's ability to adapt to the specific needs of a study, it is effective tool for making informed randomization methodology design decisions.

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W 22

Best Practices for Pregnancy Outcome Monitoring in the Post Marketing Environment

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Keywords: Best practices, pregnancy outcome surveillance, pregnancy registry

Method: Pregnancy registries are voluntary, enhanced post-marketing surveillance programs that collect health information on women who take prescription medicines or vaccines during pregnancy, and are used to inform product safety. The analysis of cumulative outcome data is provided through annual reports.

Objective: Drug and vaccine development generally excludes enrollment of women who are or may become pregnant during clinical trials. This review describes best practices for initiation, execution, and closure of pregnancy registries to detect safety signals of important pregnancy related adverse effects.

Result: A pregnancy registry may be implemented when mandated by a health authority, the product is used widely by women of reproductive age or existing data suggest a potential for harm. Pregnancy registries provide a structured approach to collect data on safety in a patient population that is exposed to prescription drugs (or vaccines) during pregnancy. Precise methods of registry enrollment and data collection are critical to ensure that complete and accurate data is obtained for analysis. Enrollment of a patient is voluntary and requires: identification of a healthcare provider (HCP); a unique patient identifier; and a documented drug (or vaccine) exposure during pregnancy. A patient or provider may decline to participate in a registry at any time. Reports are classified as prospective or retrospective. Prospective reports are those received before the outcome of the pregnancy is known; retrospective are those received after the outcome of pregnancy is known. Prospective reports comprise the primary cohort available for rate calculations. Due to inherent reporting bias concerning abnormal pregnancy outcomes, retrospective reports are analyzed separately from prospective reports. Pregnancy outcomes are ascertained from HCPs through questionnaires completed voluntarily at the time of the initial report and at the estimated date of delivery. Enhanced follow-up includes phone calls to HCP's or patients to obtain pregnancy outcome information. Efforts are made to obtain newborn and pediatric medical records. The cumulative data presented in the annual report is reviewed by a teratologist. FDA Guidelines state that a pregnancy registry should continue until sufficient information has accumulated to meet the scientific objectives of the registry or the feasibility of collecting sufficient information diminishes to unacceptable levels due to: low exposure rates; poor enrollment; or loss to follow-up. Merck collaborates with Health Authorities regarding registry closure.

Conclusion: Merck has a history of managing pregnancy registries with the highest standards of excellence. Over the past 20 years, Merck has established and supported six pregnancy registries, allowing for the collection and analysis of post-marketing data on exposures to specific drugs or vaccines during pregnancy. Post-marketing surveillance relies upon the voluntary reporting by individuals and HCPs and it is often a challenge to collect adequate data. Reports are frequently incomplete and require diligent follow-up to obtain accurate information. Pregnancy registries allow for a more rigorous collection of pregnancy outcomes. Limiting loss to follow up in prospective reports by intensive

follow up improves both the quality and quantity of the data. The annual report, with a detailed analysis of pregnancy and fetal outcomes, is provided to HCPs seeking additional information and to share with concerned patients. For example, in the varicella-containing-vaccines and human papillomavirus vaccine registries, the rates of spontaneous abortions and major birth defects were not greater than those in the general population of pregnant women in the absence of vaccine use. The information furnished by pregnancy registries allows the health care provider and patients to make more informed decisions regarding drug/vaccine use during pregnancy. Pregnancy Registry Programs serve an important public health need through the systematic collection and analysis of real world product safety in pregnancy and on fetal outcomes, and helps assure safe use of drugs and vaccines in women of childbearing age.

W 23

Use of Juvenile Animal Studies to Support Oncology Medicine Development in Children

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Keywords: Nonclinical juvenile animal studies, pediatric development of medicinal products; medicines for children

Method: Critical analysis of nonclinical information on all approved European Public Assessment Reports concerning existence of JAS, species and data from JAS in the nonclinical information on all approved paediatric investigation plans to support an oncology indication in paediatric population.

Objective: Juvenile animal studies (JAS) can contribute significantly to risk assessment and safety in paediatric clinical trials and for drug product labelling, and their usefulness will be examined in oncology medicines, primarily from a regulatory standpoint.

Result: The prediction of non-clinical models is rather limited and extrapolation of animal results to the human situation in oncology medicines should be performed with caution. The needs for early consideration of paediatric population (PP) have led to an increased focus on the relevance of nonclinical studies in juvenile animals.

Conclusion: The need for animal studies for oncology drugs is in general a matter of controversy in particular for the most severe forms and the experience for juvenile toxicity studies in advanced cancer patients is of importance. Discuss the importance and value of nonclinical juvenile animal studies for oncology medicines. Share real world experience from available historical data on juvenile animal studies towards paediatric use and build up the experience on utility of juvenile studies in therapeutic area of oncology.

W 24

Innovation in Regulatory Science: Development and Validation of an Instrument for Assessing the Quality of Decision Making

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Keywords: Quality decision-making (QDM); regulatory; instrument; devel

Method: QoDoS items were generated from Interviews with 29 key opinion leaders and content validity was established using an expert panel (Donelan et al. 2015). Psychometric evaluations (i.e. factor analysis, reliability and construct validation) were performed.

Co-Authors: Bujar, M., Donelan, R., Walker, S.

Objective: The objective of this study was to develop a standardized and validated tool (Quality of Decision-Making Orientation Scheme – QoDoS) for assessing the quality of decision-making (QDM) in medicines development and regulatory review using both qualitative and quantitative techniques.

Result: The thematic analysis of the interviews yielded a 94-item initial version of the QoDoS with a 5-point Likert scale response option. The instrument was tested for content validity using a panel of experts to rate language clarity, completeness, relevance and scaling of each item on a 4-point scale (Strongly agree to strongly disagree). The agreement among the panel members was high with an intra-class correlation coefficient value of 0.89 (95% confidence interval = .056, 0.99). A 76- item QoDoS (version 2) resulted from content validation.

Factor analysis produced a 47-item measure with four domains grouped into two parts (Part I = Organisational – Decision-Making Approach, Decision-Making Culture; Part II = Individual – Decision-Making Competence, Decision-Making Style). The 47-item QoDoS (version 3) showed high internal consistency (n = 120, Cronbach's alpha = 0.89), high reproducibility (n = 20, intra-class correlation = 0.77) and a mean completion time of 10 minutes. This suggests that the QoDoS is a practical instrument possessing strong psychometric properties of validity and reliability.

A secondary outcome of this study has been the important insights into the decision-making of 76 individuals from pharmaceutical companies (50%) and regulatory agencies (50%) who participated in a study testing the responsiveness of the QoDoS. The results showed that whilst it was recognized that the science of decision-making is important, training in this area was rarely provided. In addition all responders from agencies and 92% from companies felt that, with targeted training, they could make better decisions. The QoDoS was able to differentiate between the issues important to pharmaceutical companies and regulatory authorities.

Conclusion: Although the impact of decision-making during the development and regulatory review of medicines greatly influences delivery of new products, there appears to be no suitable instrument that can be used to assess QDM. This study has described the development and initial psychometric properties of a new tool that aims to address this unmet need using a standardised methodology.

Factor analysis was followed by construct validation, examining convergence (evidence that different measurement methods of a closely related constructs correlate) and discriminant/divergent validity (ability to differentiate the construct from other distantly related constructs) of the QoDoS. The results showed that the instrument possesses strong measurement properties of reliability and validity which should provide confidence for its use in the scenarios outlined above.

The findings of this study also provide insights regarding the decision-making approach of organisations compared with those of individuals. The QoDoS can also identify similarities and differences between regulatory agencies and companies' practices as well as areas for improvement for both stakeholders. This profiling, which

is performed as a point-in-time assessment, should allow monitoring of the changes in decision-making over time, including following specific initiatives.

The QoDoS can therefore be used to increase awareness of the biases and influences that need to be considered when making decisions, as well as the best practices that should be incorporated into a decision-making framework such as: having a systematic, structured approach to aid decision-making); assigning values and relative importance to decision criteria; evaluating internal and external influences/ biases; considering uncertainty; performing impact analysis; and ensuring transparency. Such practices underpin the FDA's recent initiative to establish "the science of therapeutic regulatory decision-making" (Edlavitch and Salmon, 2015).

W 25
Industry-Based Pharmacists and Moonlighting: Remaining Current in Clinical Practice

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Keywords: Pharmaceutical industry, pharmacy practice settings, professional development

Method: A voluntary web-based anonymous survey created through Qualtrics was distributed via email to pharmacists with a current or past affiliation with the pharmaceutical industry. This adaptive survey had a maximum of 20 questions. Question types were multiple choice, fill in the blank, and Likert scale.

Objective: To identify the rate, extent, practice setting, and reasons why licensed industry-based pharmacists moonlight (work a part-time pharmacy job) in addition to their current industry role.

Result: 108 pharmacists started the web-based survey with 101 (93.5%) completing it. Results indicated that more than half of the respondents (n=55) either currently or previously held an additional part-time pharmacist job along with their industry role. Overall survey respondents represented a variety of pharmaceutical industry departments. The majority work in departments such as R&D/Clinical Development, Field Medical (Medical Science Liaison), Marketing, Medical Information, and Regulatory Affairs. Nearly all of the survey respondents shared that they hold an active pharmacist license despite their industry employer not requiring licensure. Twenty-three percent of individuals with active pharmacy licenses hold licensure in multiple states.

Of those industry pharmacists that reported moonlighting, respondents predominantly worked in either a hospital, chain, or independent pharmacy. The average days per month worked was 3.53 (range: 0.00 to 10.00) and average hours worked per month was 22.33 (range: 0.00 to 60.00). The top four reasons for working a part-time pharmacist job included financial, keeping current, utilizing license, and patient interaction.

Out of the 55 respondents that currently or previously moonlighted, sixty-seven percent (n=37) reported that working in their alternate practice setting helps/ helped them in their industry pharmacist role. Alternatively, 64% (n=35) indicated that being an industry pharmacist helps/ helped them in their selected practice. Positive open-ended feedback on moonlighting included: higher appreciation for the job, incorporating a variety of different skills between roles, a better understanding of clinical data, ability to listen to patient concerns, gaining of competitive intelligence, and a broadening of perspective. However, other respondents listed the following unfavorable reasons: potential bias, very different environments, and no direct relation between them.

Conclusion: Pharmacists as a whole take on second jobs separate from their main source of income (moonlighting) at a greater rate than the average workforce. There is limited information in the literature about industry-based pharmacists remaining active in the practice of pharmacy. Results show that a significant number of industry-based pharmacists are licensed and many either practice in an alternative practice setting or have in the past.

This study also gained the perspective of pharmacists on how one role influences the other. Data supports that pharmacists that moonlight see multiple benefits in keeping up with active licensure and having multiple roles.

W 26
Impact of Internal Data Review and Source Data Verification on Overall Data Quality

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Keywords: Data review, risk-based monitoring

Method: An analysis of data changed as a result of the review of data at the clinical sites and internally at Seattle Genetics is presented for each of 14 studies and is further compared in two global Phase 3 trials with the key difference being the approach to reviewing the data at the sites.

Objective: The primary objective is to measure the impact data review has on the overall integrity of Seattle Genetics' clinical data on 14 oncology studies and determine if it supports recent evidence suggesting that SDV has minimal effect on data integrity (Transcelerate Biopharma Inc. May 2013)

Result: The overall data change rate averages 5.3% across the 14 studies evaluated. This includes data that may change from original entry as the result of system edit checks detecting general entry errors and as the result of data review processes that correct discrepancies. The data change rate resulting from the resource-intensive data review processes (both from source data verification and internal centralized monitoring review) averages 2.5% across the 14 studies evaluated.

A detailed comparison between the two global Phase 3 trials was performed, both of approximately the same size and complexity, with the key difference being the approach to reviewing the data at the sites. One used the industry standard of 100% SDV; the other used a risk-based monitoring approach that focused more effort on critical variables (variables identified as directly impacting study endpoints) and less on non-critical variables.

Results show minimal differences in the data change rates (2.1% vs 1.7%). This is primarily due to differences in data change rate of critical variables (3.4% vs 2.8%), with minimal impact to the data change rate for non-critical variables.

Conclusion: Of the 14 oncology trials evaluated, only 2.5% of the data changed from original entry as a result of SDV and

internal data review, supporting earlier research (Transcelerate Biopharma Inc. May 2013; Medidata Solutions. April 2012). Analysis suggests that the reduction in SDV has not impacted data quality on the global Phase 3 trial using Risk Based Monitoring. Analysis supports further expanding a risk-based approach to source data verification and to internal data review.

W 27

Is the World's Third Largest Pharmaceutical Market Ready for Patient-Centric Clinical Trials?

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Keywords: Clinical trial, members, patient advocacy group, patient support group, patient-centric, protocol

Method: In total, from 28th Sep to 16th Nov 2015, 121 patient groups were contacted in China. The groups were sent an electronic survey & followed-up by telephone or instant messages for survey completion. Of the 40 respondents, data from 35 groups interested in clinical trials were analyzed qualitatively.

Objective: This study aims to gain a better understanding of patient advocacy and/or support groups' (collectively patient groups) current landscape in China; mainly, their size, structure, experience and interest in driving patient-centric clinical trials.

Result: The survey response rate was 33% i.e., 40 groups completed the survey out of 121 contacted. Of the 35 groups (out of 40) interested in supporting clinical trials:

63% are small sized groups (with less than 1,000 members) of which
- 50% have experience in supporting clinical trials
- 82% have either a Patient Advocate or Patient Expert within their group
- 73% communicate by telephone with members on a regular basis
- 73% have regular face-to-face meetings

17% are medium sized groups (with 1,000 to 10,000 members) of which,
- 50% have experience in supporting clinical trials
- 100% have both Patient Advocate and Patient Expert within their group
- 83% communicate using digital platforms (QQ, WeiBo, WeChat, etc.) with members on a regular basis
- 83% have regular face-to-face meetings

20% are large sized groups (with more than 10,000 members) of which,
- 100% have past experience in supporting clinical trials, have both Patient Advocate and Patient Expert within their group, communicate using digital platforms with members and have regular virtual meetings in addition to face-to-face meetings.

Patient-centric activities that are of interest to more than 70% of groups per category (small, medium & large sized):
- Small sized groups: 73% are interested in sharing information/advice on specific clinical trials
- Medium sized groups: 83% are interested in referring patients to clinical trials and sharing information/advice on specific clinical trials
- Large sized groups: 80-100% are interested in supporting a continuum of patient-centric activities such as:
  - Connecting patients with biopharmaceutical companies to uncover patient insights on disease and treatment
  - Referring patients to clinical trial sites
  - Sharing information/advice on specific clinical trials
  - Working with researchers to design/improve trial protocols
  - Participating in round table consortiums with pharmaceutical companies to give feedback on trial outcome.

Conclusion: The bio-pharmaceutical industry is undergoing a paradigm shift in focus from 'product-centric' to 'patient-centric'. Patient-centricity in a clinical trial means designing and conducting a study in a way that is responsive to patient preferences, needs and values; it requires patients to be proactive in providing feedback. By incorporating patient-voices, the industry can address the greatest challenges (protocol design, enrolment delay & retention) of conducting clinical trials.

Bio-pharmaceutical companies in the US and Europe are evolving at fast pace towards patient-centricity by collaborating with patient groups. China being the 3rd largest pharmaceutical market is no different per our investigation.

There are hundreds of patient groups in China varying in size, structure and interest. Most of these groups, especially large sized are willing to broaden their horizon by supporting patient-centric activities. Creating a 'heat map' of patient groups is beneficial for bio-pharmaceutical companies as different groups may prove more valuable collaborators at different stages of the clinical trial based on their interest.

China will continue to top the list of country attractiveness index for conducting clinical trials by offering yet another benefit of conducting patient-centric trials in collaboration with patient groups.

W 28

Development of a Matching Dictionary Between Lay and Corresponding Scientific Terms to Detect Web Reported Adverse Events

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Keywords: Detection of web reported adverse events, dictionary lay language/MedDRA, pharmacovigilance tool

Method: First, we translated PT MedDRA terms in French lay language, Then, after analysis of the actual messages, the opposite approach was executed. The result was the set up of a bidirectional dictionary. The validity of the dictionary was checked.

Objective: To develop a tool to detect public web reported adverses events (AEs) formulated in lay language via the use of a specifically designed dictionnary.

Result: About 25,000 terms in lay language have been linked to 1,000 PT MedDRA terms. The approach has been implemented upon request of an official body for three products (A, B, and C) with well-known safety profiles as described in the FAERS and MedEffet databases. An algorithm was designed to capture the adverse events in the messages and to translate the latter with the help of the dictionary. More than 4,000 web messages from close to 300 websites were analysed.

1. For Product A, the 15 leading adverse events described in the reports of the authorities have been detected on the Web messages and were correctly translated in PT MedDRA terms. Quantitatively, the frequency of the occurrence of adverse events displayed differences between lay and official reporting. Subjective and harmless side effects (e.g. weight increased) were

reported more frequently on the Web. The results obtained with the algorithm were monitored by analysing all Web comments related to the Product A. Adverse events of nearly 90% of messages citing the Product A were correctly translated. Noteworthy, the algorithm was able to detect an unlisted event in the European SPC.
2. For Product B, adverse events described in the reports of the authorities have been detected on the Web messages. In addition, the algorithm was able to detect several cases of misuse (1.5%).
3. For the Product C, adverse events described in the reports of the authorities have been detected on Web messages. In addition, the algorithm was able to detect numerous off-label prescriptions (32%).

Conclusion: The use of our unique matching dictionary of patient lay expressions/wordings and PT MedDRA terms for our tool identifying adverse events on Web messages allowed us to reliably detect known adverse events but also new unlisted adverse events in the SPC and pharmacovigilance circumstances.

Unlike scientific language, lay language is constantly changing which requires a work intensive and continuous enhancement of the dictionary by a group of professionals in pharmacovigilance.

The use of this entirely original dictionary has enabled the development of a reliable tool not only for the characterization of adverse events reported on the Web messages but also to early detect misuse and off-label use making it a useful and valuable patient centric additional approach for pharmacovigilance activities.

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W 29

SC Influence on the Cost of Conducting Clinical Trials and Impact on Pricing of Related Services: Evidence from a Pilot Study

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Keywords: Clinical research associate, costs, CRA, influence, monitoring, SC, study coordinator, time

Method: Analysis of time coded/pt. recruited by 8 CRAs across 10 projects, 30 project sites and 3 countries.

Objective: Compare the monitoring time spent per patient (pt.) recruited (onsite, offsite/remote) by the same Clinical Research Associate (CRA) for that very project at 3 different sites supported by different SCs.

Result: The data showed that "Good" SCs reduced Clinical Research Associates' (CRAs) monitoring time (onsite and offsite/remote) by 50%. Attributes of "Good" SCs were identified through in-depth qualitative interview with CRAs, and reinforced by a survey of 200 CRAs, of which 133 responded to these two questions 1) "Whom do you consider as 'Good' SCs?" 2) "What do they do that others don't do?" The data analyzed to determine monitoring time differences included time coding across seven categories. To rule out bias, only those projects in which the same CRA monitored at least three different sites in the same project were considered. While it is well known that SC capabilities, proficiencies and cooperation level are likely to drive the monitoring efficiency, this study provides quantitative evidence regarding SC's influence on time spent by a CRA on different aspects related to monitoring.

Conclusion: A 50% reduction in monitoring time is a strong indicator of SC influence on the direct costs of monitoring besides the influence on indirect costs which include timeliness (startup, CRF completion, data query resolution, action items), patient recruitment, retention, compliance, data quality and data integrity. Reduction in onsite monitoring days for a CRA will also reduce the travel costs. SC efficiency would translate into optimal utilization of staff at a site reducing the personnel related costs for the sites and hence the overall pricing at a site level. With the increasing use of Risk Based Monitoring (RBM) which determines the pricing of clinical trial related services, SCs will continue to have ever-increasing influence. These results warrant thinking around the overall hands on training and development of SCs besides Good Clinical Practice (GCP). It also provides quantitative evidence on significant Return on Investment (ROI) for the Sites as well as the Industry to improve SC proficiency with appropriate intervention.

W 30

Implementing Neurocognitive Testing in Clinical Trials: Facilitating Rater Administration With an iPad-based App

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Keywords: Brief assessment of cognition (BAC), clinical trials, iPad app, neurocognitive testing, schizophrenia

Method: 48 patients (23 female) with schizophrenia and 50 healthy controls (25 female) were recruited from 3 US academic sites. Participants were assessed with both the pen-and-paper Brief Assessment of Cognition (P&P BAC) and the iPad-based application (BAC App), in a counterbalanced order.

Objective: To determine the validity of a newly-developed iPad-based App to facilitate test administration of an established neurocognitive test battery in clinical trials of challenging patient populations.

Result: In both groups, the distributions of standardized composite scores for the P&P BAC and BAC App were indistinguishable, and the between-methods means were not significantly different. Discrimination was similarly robust, with the P&P BAC (d=1.24) and BAC App (d=1.34) both demonstrating large effect sizes of deficits in patients compared to controls. The between-methods correlations for individual measures in patients were r>.70 except Token Motor (r=.43) and Tower of London (r=.61). In patients, performance between the test methods was not significantly different on any test, except the Token Motor Test, where the mode of performance is qualitatively different. When data from the Token Motor Test were excluded, the correlation of composite scores improved to r=.88 (p<.001) in healthy controls and r=.89 (p<.001) in patients, consistent with the test-retest reliability of each measure.

Conclusion: To facilitate the administration of a widely-used pen-and-paper neurocognitive battery, the Brief Assessment of Cognition (BAC), we developed an iPad-based application, the BAC App. The purpose of the BAC App is to reduce administration burden on site raters by automating and standardizing the testing procedures and scoring, while maintaining the importance of the rater-patient interaction. Ensuring full understanding of

the task at hand, motivation to try their best, and providing general encouragement to complete the testing is critical to obtaining meaningful data in impaired or behaviorally-challenging patient populations such as Alzheimer's Disease, depression, ADHD and schizophrenia. The data from this validation study confirm the equivalence of the mode of administration between the P&P BAC and BAC App for all subtests, except Token Motor. The applicability of the established normative data is also confirmed. Therefore, tablet-assisted rater administration using the BAC App is a viable option for use in future clinical trials to reduce site burden while maintaining the validity of the neurocognitive outcomes.

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W 31

Impact of Biosimilars in Clinical Practice and Clinical Research: Results of Questionnaire- Based Survey

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Keywords: Biosimilars

Method: For this study we reviewed available literature regarding regulations related to Biosimilar drug dev. & biosimilar prescription around the world. We also conducted a global survey to physicians from various specialties to understand the factors involved in prescribing biosimilars in their practice.

Objective: The objective of this study is to analyze the trends observed in biosimilar drug prescriptions amongst treating physicians and their interest towards biosimilar drug development.

Result: The majority of the physicians were aware of the term "Biosimilars" and had good understanding about the process involved in developing biosimilars. The preliminary results of the study indicate that there is interest being shown in prescribing biosimilars in regions where biosimilars are available. Various factors including patient's discretion were the primary reason for prescribing biosimilars. Oncology, autoimmune disorders and endocrinology were the major disease segments in which biosimilars are prescribed as per the study. Keen interest was shown in participating as investigators in clinical trials involved with biosimilars. There is strong opinion amongst physicians that Biosimilars must be compared to originator molecules in clinical trials to determine efficacy and safety parameters.

Conclusion: There is steady increase in usage of biosimilars amongst treating physicians across the globe. While there are certain concerns with availability and regulations in certain regions, biosimilars are slowly being preferred for their cost effectiveness in various debilitating disease conditions. With the number of clinical trials related to biosimilars on the rise, more physicians are beginning to understand that biosimilars are unique molecules in comparison to generic drugs. More resources need to be provided by pharmaceutical industry for training the physicians and patients on better understanding of efficacy and safety of biosimilars.

W 32

Geo-Political Analysis of Phase 3 Clinical Trial Recruitment: Changes in 2015

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Keywords: Analytics,Big data, Biopharmaceuticals, clinical trial geography, clinical trials, clinicaltrials.gov, Data evaluation, data visualization

Method: The information housed at the web site www.clinicaltrials.gov (CT.g) was downloaded and "cleaned", using filtering and logic processes. This data was evaluated in an analytics software to evaluate the annual number of Ph3 studies conducted and the number of countries recruiting subjects.

Objective: This study evaluates the changes in geographical locations of sites recruiting subjects in Phase 3 (Ph3) study sites in 2015 compared to the previous 5 years.

Result: The dataset from CT.g was filtered to identify only Ph3 studies sponsored by industry and then filtered for the years from 2010 to 2015. The numbers were 1089, 1089, 1035, 959, 982, 944, in 2010, 2011, 2012, 2013, 2014 and 2015 respectively. The mean number of subjects per trial was 601, 517, 593, 639, 549, 529 respectively per year. It was anticipated that the number of countries used for recruiting subjects per year would remain consistent whereas it decreased significantly in 2015.

Taking the mean (and median) number of countries used in phase III studies where there are sites in >1 country, there was a decrease in 2015 compared to previous years. The mean (median) number of countries in 2015 was 10.19 (8) compared with 11.23 (9) for the five previous years.

A geographical "heat map" was generated to evaluate if there were obvious changes or if this was a random event. It was apparent that there were three distinct geographies that were not used in 2015; The middle east centered on Syria, Africa and South America.

Middle Eastern studies: In the years 2010 to 2014 there were on average 114 studies conducted in this region. In 2015 this declined to 93 studies. It is presumed that due to the significant conflict of the area centered on Syria, that sponsors declined to initiate studies in this region.

African Continent: In the years 2010 to 2014 there were on average 94 studies conducted in this region. In 2015 this declined to 53 studies. It is presumed that due to the significant conflict of the area centered on the Northern countries of this continent, that sponsors declined to initiate studies in this region.

South America: In the years 2010 to 2014 there were on average 173 studies conducted in this region. In 2015 this declined to 101 studies. It is surmised that there maybe a number of factors: including some political instability, the cost of doing business and the rise in the zika virus and the perceived health risks associated with the area.

Conclusion: This study provides a number of useful insights into the geopolitical aspects of recruiting subjects into multi-center, multi-country Ph3 clinical trials. With careful use of analytics and the information from CT.g it was possible to ascertain the decrease in countries and locations where study subjects are being recruited. It is the

first time in 6 years we have observed a decline in countries where clinical trials have been conducted. While it was not part of this study, the same effect was also noted in other phases of clinical trials from the same data set.

This suggests that the international political changes may have a profound effect on the recruitment of clinical trial subjects. More countries have been involved in subject recruitment to provide access to either unique, naive or just larger pools of subjects for Ph3 industry sponsored trials. This study does not provide information as to whether recruitment rates are decreasing or whether it is possible to recruit the same subjects in a smaller geographical spread with a stronger focus.

The authors have provided a reasonable hypothesis as to the reason for the decrease in the number of countries participating in PH3 studies, but further work will be required to confirm these findings. The other limitations are that it is assumed that all Ph3 studies are registered on CT.g to ensure publication rights are available for obtaining the NCT number.

In conclusion, data analysis and carefully curated analytics has provided clear insight into the decrease in investigator sties in 2015 on a global basis. It has allowed the geographical changes to be easily highlighted and it now needs to be evaluated if this is a change in a single year or a clear change in the country locations of clinical trials.

W 33

A Comparison of Single-Dose Pharmacokinetics Studies in Subjects with Various Degrees of Renal Impairment

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Keywords: Biostatistics, clinical trial, pharmacokinetic, renal impairment

Method: Compare conduct and analysis from protocol to results of 2 renal impairment trials. Study F5 was designed as a full renal impairment study while trial M9 was a reduced PK study. Moderate and severe impaired patients were enrolled at a hospital site;mild impaired and normal subjects at the CRO site.

Objective: To evaluate and compare the impact of different types of designs on study start-up and reporting activities in renal impairment trials.

Result: Study F5 was a full PK study in patients with mild, moderate, and severe renal impairment compared to normal subjects. Study M9 was an adaptive trial conducted first in patients with severe renal impairment and subjects with normal renal function using a reduced PK study design. Moderate renal impaired patients were enrolled subsequently based on safety data and substantial changes in drug exposure. Protocols were reviewed by the hospital and CRO investigators and finalized within 13 days for F5 and within 15 days for M9. The average timeline of the studies from submission to approval was 30 days for the hospital IRB, and 10 days for the central IRB. The NOL from Health Canada was issued < 30 days after submission of the CTA for both trials. The First Patient In (FPI) was within 3 weeks of regulatory approvals for study F5, and within 2 weeks for trial M9. The duration of the trial in study F5 was 6 months, while it was 4 months in the reduced design trial M9 (FPI to Last Patient Out (LPO)). Noncompartmental PK analysis was performed and a regression analysis was used to evaluate the relationship between renal function and the PK parameters. If the correlation was significant, an ANOVA was performed. The PK and statistical results were completed 15 days after reception of concentrations values for study F5. In study M9, results were provided faster after the first two groups in order to assess promptly the need for the moderate group. Final analyses were available 20 days after reception of concentrations values.

Conclusion: The 2010 FDA guidance on renal impairment provides recommendations on the design and conduct of pharmacokinetics studies in patients with impaired renal function. The impact of renal impairment on the pharmacokinetics of a drug can be determined with a reduced PK study design, comparing subjects with normal renal function and patients with severe renal impairment. A full renal impairment study in patients with intermediate levels of renal impairment is then conducted if differences in the pharmacokinetic profiles are observed. Some companies also decide to develop projects as a full study from the beginning.

Multiple factors can influence the study start-up period of a clinical trial, and also availability of the final report at the end of a study. However, the approach to describe the impact of renal impairment did not seem to influence these activities. Current enrolment data were compared to selected studies on ClinTrial.gov, which were completed and included matching healthy subjects to evaluate the impact of renal impairment on a pharmacokinetic profile of a drug. The analysis included a total of 71 studies performed between 2012 to 2015. The FPI to LPO timeframe lasted on average for 213 calendar days. Our multi-center approach permitted to lessen this timeframe to 181 days for F5 and 122 days for M9.

W 34

Urodynamic Measurement of Urethral Closure Function in Healthy Japanese Women: A Single Dose Study of Duloxetine

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Keywords: Healthy Japanese women, stress urinary incontinence, transcranial magnetic stimulation, urodynamics

Method: The urethral pressure profiles at rest and the motor threshold (MT) for urethral sphincter contraction in response to transcranial magnetic stimulation (TMS) were measured before and 6h after the administration of 40 mg duloxetine in 10 healthy female subjects (Ages: 20 to 55 years old).

Objective: This urodynamic study in healthy Japanese women was performed to evaluate the effects of duloxetine, the SNRI for urethral function, and to determine an appropriate method for making go/no-go decisions in early drug development to treat stress urinary incontinence (SUI).

Result: The demographics of female subjects in this study had a mean age of 21.6 years and a mean body mass index of 19.4 kg/m2. The procedures were well tolerated by all subjects. A single oral dose of duloxetine significantly increased the mean and maximal urethral closure pressure at rest calculated over the entire urethra. When the functional urethral length was divided into three sections, duloxetine significantly increased the mean and maximal urethral closure pressure at rest over the proximal and middle-third of the urethra. The individual MTs for urethral sphincter contraction in response to TMS were determined as the minimum intensity

that produced urethral pressure spikes and were expressed as a percentage of maximum stimulator output. None of the subjects reported any pain or discomfort during magnetic stimulation at the midline over the cranial motor cortex. The individual MTs for urethral sphincter contraction in response to TMS were able to be determined in all subjects at both baseline and follow-up with duloxetine. An oral administration of duloxetine significantly lowered the MT in response to TMS (61.5% vs. 72.0%, p = 0.02).

Conclusion: Pharmacological targets for the treatment of SUI include adrenergic receptors in the urethral smooth muscle and serotonergic receptors in the spinal cord. Thus many new drugs, specifically designed for these receptors, are currently under development for SUI. In this urodynamic study, urethral closure pressure at rest was measured to evaluate the drug effects on urethral smooth muscle. Furthermore, because the nerve endings from the central nervous system terminate at Onuf's nucleus and synapse with the pudendal nerve, the MTs in response to TMS were determined in healthy Japanese female subjects for evaluation of drug effects on Onuf's nucleus in the spinal cord. Our data indicated the facilitatory effects of duloxetine, a serotonin and noradrenaline reuptake inhibitor, on the noradrenergic pathway-mediated smooth muscle functions and the contractions of the urethral striated sphincters via Onuf's nucleus. It is thus reasonable that the proposed method is potentially useful to reduce the attrition rate by providing decision-making data in early clinical studies of new drugs being developed to treat SUI.

W 35
Comparison of Manual Versus Automated Redaction Techniques for Clinical Submission Documents

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Keywords: Clinical study reports, disclosure, EMA policy 0070, redaction, transparency

Method: A clinical study report was redacted using both a manual and automated process. Quality and efficiency measures calculated for both processes was measured and compared.

Objective: This study analyzed the quality and efficiency of a primarily manual redaction process using Adobe Professional software compared to an automated process using advanced commercial redaction tools

Result: Redaction of the clinical study report using the manual process that included manual scientific review of the report and redaction using only basic redaction tools and standard functionality of Adobe Professional v.10 took significantly more total process time (more than 50%) than the automated process, which used advanced commercial redaction software followed by data cleanup and manual scientific review. The manual redaction process produced significantly fewer total initial redactions (~7 times less) and no false hits, largely because of the limited availability of automated searching functionality to systematically detect keywords related to company confidential information, patterns in the text related to subject numbers, personal contact information such as email addresses, addresses and telephone numbers or dates in the document text using only Adobe Professional. Because the automated process produced a pre-redacted report based on the advanced keyword, string and pattern searching, false hits that subsequently required cleanup and removal were prevalent with the automated process. Quality, measured by total number of errors/omissions identified during a manual quality review step, was similar regardless of the redaction method used. This indicates that overall quality was not reduced when using the automated process, despite the dramatic decrease in total process time. Quality was improved with the automated process when input from the SDTM datasets for key variables such as subject identifier, lot/batch numbers, staff names and contact information, treatment dates and medical history and physical examination terms were used as input to the commercial redaction software tool. However, this approach required the most time up front related to gathering study and product specific requirements and input into the commercial software tool and produced the most false hits, particularly related to medical history and physical examination terms.

Conclusion: The most effective and efficient process for redaction of clinical submissions documents appears to be a hybrid approach which uses an advanced commercial redaction tool with input from the SDTM datasets for key variables, followed by full scientific review and quality control. This hybrid process ensures that powerful automated text searching algorithms are used to search out potential areas for redaction based on the known key inputs, producing a pre-redacted report that can be then reviewed manually by a trained scientific reviewer and quality control analyst to ensure that variations in presentation of material in the report that are difficult to predict and program into an automated tool are not missed and that false hits produced by the automated tool are removed or adjusted as needed. While Adobe Professional includes adequate tools for performing redaction, it does not include many of the advanced text and pattern searching features that are present in the advanced commercial redaction tools that are available on the market that make complicated text, string and pattern searching much more automated and precise. Most commercial redaction tools surveyed for this study include functionality to easily include SDTM output into redaction algorithms and the results seen in testing were promising. Further exploration into the synergies that can be gained by performing data anonymization and clinical document redaction in parallel is needed to determine the full extent of the efficiencies that can be achieved.

W 36
The Influence of Atipic Antipsychotic Drugs on Vas Deferens in Mice

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Keywords: Antipsychotic drugs, risperidone, olanzapine, quetiapine

Method: Male mice were treated by ip injection of drugs during 21 days. Then, the effects of saline, quetiapine (5 and 10 mg/kg), olanzapine (1 and 2 mg/kg) and risperidone (0.25 and 0.5 mg/kg) were investigated on serotonin and KCl-induced contractile responses in isolated vas deferens strips.

Objective: Beside dopamine, serotonine is the second important neurotransmitter to influence sexual dysfunction. Serotonin mainly inhibits sexual function by stimulating postsinaptic 5-HT2A and 5-HT2C receptors. Implications for future research; atipic antipsychotics should be strongly taken into account.

Result: Serotonin-induced contractile responses were significantly increased in the epididymal and prostatic portion of the vas deferens obtained from the risperidone-

treated group. The Emax value for serotonin was significantly higher in prostatic and epididymal portions of the mice vas deferens obtained from risperidone-treated group than control group. However, olanzapine and quetiapine treatment had no effect on serotonin responses in both epipdidymal and prostatic portions of mice vas deferens. There were no significant differences in KCl-induced contractile responses among the groups.

Conclusion: Risperidone but not olanzapine and quetiapine could impair sexual competence in male mice. Serotonergic purinergic receptors may, at least in part, contribute to changes in vas deferens contractions in mice with chronic treatment of risperidone but not olanzapine and quetiapine. This study will help clinicians make a purpose-oriented choice of which antipsychotic drug to use.

W 38

Patient Preference for Electronic Patient Reported Outcomes: Assessment in Patients with Psoriatic Arthritis (PsA)

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Keywords: ePRO, preference, psoriatic arthritis

Method: To establish equivalence of P and E versions of 7 PROs in PsA patients, a randomized, crossover equivalence study was conducted. After patients (N=53) completed the P and E versions of each PRO, they completed a survey on ease of use, acceptability and preference for the P and E versions.

Objective: To provide evidence of patient acceptance and preference for electronic PROs in patients with PsA, this poster will describe results of acceptance and preference surveys collected in the context of a randomized, crossover paper (P) – electronic tablet (E) mode equivalence study.

Result: Equivalence of Paper and Electronic PROs: Intraclass Correlation Coefficients ranged from 0.75 to 0.97, all above the generally accepted threshold of .70. T-tests revealed no significant mean difference between P and E scores, and mean score differences between P and E measures were small and within an acceptable limit of equivalence.

Patient ease of use, acceptability and preference for Paper and Electronic PROs: Patient ratings of acceptability were high for both tablet (52; 98.1%) and paper (50; 96.2%) and few patients reported problems using the tablet (2; 3.8%) or paper (4; 7.6%). Patient quotes suggest some problems may have been directly related to patients' PsA. Although they did not report difficulty using the stylus to respond to questions on the tablet, patients did express concerns about holding a pen to complete the paper: "My handwriting is not as good and my hand was getting tired due to the arthritis and little painful and stiff"; "Holding a pen becomes difficult over time"; "Discomfort in hands at times with pen." Patients reported additional difficulties related to vision for both the tablet and paper versions. In reference to the tablet, two patients reported having to move the tablet to avoid glare from overhead lighting. With regard to paper, one patient noted: " I have trouble reading paper for a long time."

Despite similarities in ratings of acceptability for the tablet and paper, the majority of patients (45; 84.9%) reported that the electronic tablet was 'very easy' to use, while fewer than half (23; 44.2%) reported the same rating for paper (p<.001). The majority of patients (37; 74%) preferred the tablet to paper, while 12 (24%) had no preference, and only 1 (2%) preferred paper. Patient quotes reflect the general acceptance of the tablet, and the preference for it over paper: "I think everyone should use one; it's very easy to use."; "It's easier, faster, comfortable."; "Much easier than the paper to use."

Conclusion: Although results indicate that the PRO scores are equivalent when administered to patients with PsA via electronic and paper modes, tablet versions may be a more viable option for use in clinical trials with PsA patients. Patient reports of specific problems holding a pen or writing for long periods of time suggest that electronic tablets may reduce the burden of data collection on PsA patients in clinical trials, and patients rated the tablet version to be easier to use, and reported a clear preference for it over paper. These results support the use of the electronic tablet versions of PRO measures in PsA clinical trials.

W 39

Novel Use of a Medication Event Monitoring System to Track Rescue Medication Use in a Trial of a New Meloxicam Drug Product

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Keywords: Analgesia, clinical method, medication event monitoring system, MEMS, rescue medication

Method: Acetaminophen rescue medication use was measured using a bottle equipped with an electronic MEMS cap. Continuous data collection enabled the following analyses by trial day and time of day: number of rescue events, time to first rescue event and proportion of subjects with rescue events.

Objective: To describe use of a Medication Event Monitoring System (MEMS), as an alternative to patient diary cards, to track the timing and patterns of rescue medication use for evaluating persistence of efficacy of a new low-dose meloxicam drug product in a trial of patients with osteoarthritis pain.

Result: Subjects treated with meloxicam required substantially less rescue medication compared with placebo, unrelated to the time of day or duration of treatment. Subjects treated with meloxicam required rescue medication on fewer days (P=0.0007) compared with placebo. Among subjects who received trial drug for more than 2 weeks, a gradual decrease in the amount of rescue medication use was observed with increasing trial duration. A lower proportion of patients treated with meloxicam required rescue medication for all time of day intervals compared with placebo, suggesting persistence of efficacy. Overall, standard rescue medication accountability (pill counts) overestimated the number of rescue medication doses recorded using MEMS bottle opening events (P<0.0001).

Conclusion: Use of MEMS was successful in assessing rescue medication use in a placebo-controlled trial that measured analgesic efficacy and addressed the common challenges associated with unreliable data recording in standard diary cards and the inadequacy of standard drug accountability to provide details on the timing of rescue medication. MEMS was found to provide reliable and rich electronic dosing data records over this 12-week, Phase 3, randomized controlled trial. Analyses of rescue medication usage

by time of day suggested persistence of efficacy throughout the 24 hour dosing interval for this new low-dose meloxicam drug product. MEMS, generally considered the gold standard for measuring medication adherence in patients with HIV, asthma, and hypertension, represents a promising new approach for the collection of rescue medication data. Future outpatient analgesic trials may benefit from utilization of MEMS to enhance collection and analysis of data on rescue medication usage.

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W 41

Engaging Patients with eClinical Technology: Incorporating Patient Preferences into Osteoarthritis Management and Care

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ERT

Keywords: eClinical technology, patient engagement

Method: Subjects aged 37-90 with OA (n=104) were surveyed as part of a mode equivalence study. Subjects answered questions regarding their level of familiarity and use of technology, as well as preference for using eClinical technologies to improve physician communication and disease management.

Objective: An important characteristic of successful healthcare and clinical trials is strong communication between patients and providers. This study examined preference among subjects with osteoarthritis (OA) for communication and disease management using electronic clinical (eClinical) technology.

Result: Subjects were diverse in age, sex, ethnicity, and technology use. 50% of subjects reported having a computer at home, and 48% reported using the internet daily. 35% of subjects use email on a daily basis, and 21% use email weekly. The majority of subjects (72%) were interested in using electronic methods to interact more with their physicians between visits to help manage and treat their disease. Subject preference for modes of electronic interaction included email (60%) or text message (51%) communication with their healthcare providers, and medication reminders (38%) or clinical visit scheduling (32%) on a smartphone. Overall, subjects thought the most effective way of improving and managing their health is to increase communication and interactions with their physicians (34%) and monitor their symptoms and medications electronically (39%). Subjects reported that having more knowledge about OA would make them more likely to discuss their quality of life (44%) and symptoms (40%) with their physicians.

Conclusion: Subjects with OA are interested in using electronic methods to increase communication with their physicians and manage their disease. eClinical technology is a way to optimize patient engagement and provider communication. Incorporating eClinical technology may lead to increased patient compliance and ultimately improve clinical care.

W 42

Adaptive Design in Dose Selection Study of Next-in-Class NNRTI

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Keywords: Adaptive design, clinical trial, HIV, next-in-class, NNRTI, VM-1500

Method: Randomized clinical trial of VM-1500 was conducted at 13 Russian sites. VM-1500 20 mg, 40 mg, and EFV were studied at Stage 1. Optimal dose of VM-1500 was selected based on viral load at Week 12. Additional patients were enrolled at Stage 2 to demonstrate non-inferiority of VM-1500 vs. EFV.

Objective: Adaptive two-stage design with interim analysis for dose selection was used in Phase 2-3 study of new NNRTI VM-1500. The study objective was to select the optimal dose of VM-1500, and evaluate its efficacy and safety vs. Efavirenz (EFV) in combination with 2NRTI in treatment naïve patients with HIV.

Result: The primary efficacy endpoints were the decrease of viral load <400 copies/ml by Week 12 (Stage 1) and <50 copies/ml by Week 24 (Stage 2). Safety endpoints included CNS adverse events of special interest (AEOI).

90 patients were randomized on VM-1500 20 mg, 40 mg, or EFV at Stage 1 (1:1:1 ratio). 30 (100%) patients on VM-1500 20 mg, 28 (93.3%) patients on VM-1500 40 mg, and 24 (80%) of patients on EFV competed 12 weeks of treatment. The target viral load of <400 copies/ml at Week 12 was achieved by 28/30 (93.3%) on VM-1500 20 mg, 25/29 (86.2%) on VM-1500 40 mg, and 22/27 (81.5%) patients on EFV. The difference between study groups and EFV was 11.8% for VM-1500 20 mg and 4.7% for VM-1500 40 mg; corresponding 95% CI lower bounds were -2.6 and -11.5% (both to the right of the non-inferiority margin d = -15%). Mean change of viral load (log10) at Week 12 was -2.9 on VM-1500 20 mg, -3.2 on VM-1500 40 mg, and -3.0 on EFV. AEs were reported in 21 (70.0%) patients on VM-1500 20 mg, 25 (86.2%) patients on VM-1500 40 mg, and 24 (85.7%) patients on EFV; AEOIs were reported in 6 (20.0%) patients on VM-1500 20 mg, 11 (37.9%) patients on VM-1500 40 mg, and 15 (53.6%) patients on EFV. Based on the primary efficacy endpoint assessment (<400 copies/ml in 93.3% patients) and the best safety profile with regards to AE and AEOI rate, VM-1500 20 mg was chosen for further investigation at Stage 2.

The additional interim analysis showed that among Stage 1 patients, 30 (100.0%) patients on VM-1500 20 mg and 23 (76.7%) patients on EFV competed 24 weeks of treatment. The target viral load of <50 copies/ml at Week 24 was achieved by 28/30 (93.3%) on VM-1500 20 mg and 19/27 (70.4%) patients on EFV. The difference between study groups was 23.0% with 95% CI lower bound 2.9% (to the right of the non-inferiority margin d = -15%). The preliminary results show potential to demonstrate not only non-inferiority, but also statistically significant difference between groups in the final analysis.

Conclusion: Adaptive clinical trial design refers to studies that allow modifying any design or hypothesis aspect based on the interim data analysis. Any adaptation is appropriate solely in accordance with the predefined plan and at preselected time points. Although adaptations in dose selection studies are still considered less-understood, its methodology can be

successfully introduced in clinical programs of next-in-class drugs.

Next-in-class drugs are original patented medications with known targets which are similar to existing drugs in structure and mode of action. This allows for higher predictability of drug effects in humans, and possible achievement of better clinical results owing to the «fine-tuning» of the original molecule. Looking back over the complexity of the clinical paths of original innovative medications, the next-in-class drugs deserve shorter timelines and less expensive development.

Low-risk R&D strategy for the next-in-class drugs is justified by abundant clinical data of medications of the same pharmacological class that support the choice of predictable endpoints, non-inferiority hypothesis, accurate sample size calculation, and well-studied control.

Implementation of adaptive design in Phase 2-3 study of the new NNRTI VM-1500 requires significantly lower sample size and shorter timelines for testing the non-inferiority hypothesis vs. standard of care treatment with EFV in combination with 2NRTI as opposed to similar studies of earlier drugs of the same class. The adaptation includes the choice of optimal dose of the study drug for the second stage of the trial based on the interim analysis of efficacy and safety. Potential biases are controlled by dose blinding design and DMC for assessment of efficacy and safety endpoints. No changes to the initial statistical assumption and methods will be implemented during the trial.

Justified and tailored adaptive design can be recommended for clinical development of next-in-class drugs.

W 43

Pooled Continued Access Protocol for Oncology Experimental Therapeutics No Longer in Development

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Keywords: Clinical trial, oncology, patient benefit, protocol

Method: To provide patients with access to therapy, clinical trials traditionally remain open collecting data long after achieving primary endpoints and completing final study reports. The associated resources, operating costs and regulatory requirements can continue for years for these clinical studies.

Objective: Experimental agents that have been discontinued from development often still have patients that are on study and receiving long term benefit. Although it is a fortunate problem to have, managing these patients becomes challenging since the development of the agent has ended.

Result: We have designed and executed a single, master protocol (NCT02632994) which allows multiple experimental agents that are no longer in development to be rolled into single agent addenda serving as study "arms." This provides patients continued access under one protocol instead of under multiple protocols in various programs. By utilizing this novel protocol approach, there is a significant cost/resource savings and improved oversight and management of these cancer patients. This approach allows for continued patient benefit through uninterrupted supply of the experimental agent, and ensures appropriate, required safety monitoring and data reporting, while reducing costs associated with clinical studies.

Conclusion: This achieves a balance of meeting patient needs while allowing valuable resources to be redirected toward more promising experimental assets currently in development.

W 44

Social Listening for a New Product Launch and Beyond: How Does the Conversation Change Over Time?

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Keywords: Adverse events, benefit:risk, drug safety, pharmacovigilance, social listening, social media

Method: We reviewed de-identified English language social media posts from Facebook, Twitter, and several patient forums for a pharmaceutical product approved and launched in 2011. Each post was manually classified for its content, and results were summarized by quarter years.

Objective: To describe characteristics of conversations in social media surrounding a new pharmaceutical product during the first four years of the product's life cycle.

Result: We reviewed 4,095 social media posts from 1Q2011 around the time FDA approval was first obtained through 16 September 2015. Posts were provided and deidentified by a third party vendor searching under trade and generic names as well as common misspellings, then divided into quarters by months and curated by a team of trained health care providers. Each post was tagged if it belonged into one or more of 4 categories: adverse events, posts seeking information/asking a question, positive benefit discussions, and lack of effect discussions.

Over the first two years on the market, discussions of all four of these categories ranged from 0 to 43% of total mentions of the product across data sources. After two years on the market, however, these category ranges became much narrower and at lower rates, ranging from 1 to 18%. Specific numbers for adverse events were 14-43% in the first two years and 8-15% after two years; seeking information posts were 11-33% first two years and 8-18% thereafter; positive benefit discussions were 0-25% first two years and 7-16% thereafter; lack of effect discussions were 0-11% first two years and 1-4% afterwards.

Another interesting trend was in the overall volume of product discussions on Facebook, Twitter, and patient forums (dailystrength.org, healingwell.com, healthunlocked.com, and three indication-specific sites) over that same time period. The general trend was for discussions to take place most commonly on the indication-specific patient forums near launch, with Twitter picking up just over one year after approval and Facebook gaining more volume at around two years post-approval. Specifically, patient forums accounted for 80-100% of posts from 1Q2011 until 2Q2012, when Twitter accounted for 41% of the total volume. Twitter then stayed at above 40% for the remainder of the project while forums fell to under 20%. Facebook increased to 52% of the volume in 2Q2013, and remained primarily between 20 and 50% thereafter.

Conclusion: With social media continuing to rise in popularity as a communications tool, pharmacovigilance experts are striving to understand online discussions as a data source that might augment the current tools in use for drug safety surveillance. For this particular product, we showed a quite striking leveling out of social media

discussions (as a percentage of total drug mentions) surrounding adverse events, information sought, positive benefit, and lack of effect at two years post-approval, which was sustained over nearly three years of continuing data. Clearly the findings may not be generalizable since this is the only product for which we currently have these data available. We are actively considering other new products on which to attempt replication of these results. If this general trend were true across many different products, it might serve as a baseline rate to aid in the identification of unusual spikes in the frequencies of discussions of these important events. This could be one of many steps necessary in pursuit of an automated approach to using social media listening for pharmacovigilance.

The second trend we noted involved detecting where the highest volume of posts were found over time (first in patient forums, then in Twitter and ultimately increasing in Facebook) which may help to quickly locate the bulk of early discussions in social media. Further research is needed to determine if either of these trends is generalizable, and to further characterize the nature of discussions on social media. The ability to automatically tag or classify posts will be key to increasing the scalability of the use of this technology.

W 45

Real-Time Monitoring of the Digital Patient in Clinical Trials

Gregory Zak
ICON

Keywords: Clinical outcomes, digital patient, remote monitoring, wearable devices

Method: Wearable and patient-centric mobile technologies from multiple vendors were used to collect typical clinical outcome measures from healthy volunteer subjects. The data were integrated into an informatics hub using a digital health platform vendor for central analysis alongside subject variables.

Co-Authors: Marie McCarthy, MSC, MBA, Director, Product Innovation, ICON; Louis Smith, BAI, MSc, Data Science Manager, ICON; Willie Muehlhausen, DVM, VP Head of Innovation, ICON

Objective: Wearable technology is a key component in the design of more patient-centric clinical trials, and this poster reports the real-time monitoring of subjects using wearable and patient-centric devices from multiple vendors.

Result: Wearables and sensors are now commonplace, with 70% of consumers aware of wearable technology and 1 in 6 owning a device. Most of these devices sync with mobile phone apps, which in turn upload the data automatically to the cloud. The need for patients to travel long distances to attend site visits can be replaced by a "virtual site visit" in the patient's home. We have shown how the virtual site visit can even be continuous, delivering clinically relevant data that track safety and protocol compliance in real time. The implementation of this innovative approach requires careful consideration and planning, not only in terms of the selection of suitable, FDA-approved devices but also with respect to data management and analysis. We used some commercially available, validated devices to collect data from volunteer subjects, who synced their data with an associated vendor app on their phones. We then provisioned each user using a unique and secure token in a digital health platform vendor, allowing them to authorize the transfer of their data from the primary vendor. We built a custom integration tool to pull the data from the digital health platform API into our own informatics hub, where we integrated the data with solutions for risk-based monitoring, safety monitoring, protocol compliance and subject engagement. All data held in the cloud were completely non-identifiable, but we were able to re-identify the data once they arrived in our local and secure informatics hub.

Conclusion: The sustainability of the current drug development model is under serious scrutiny, with increasing costs, time to market and complexity and a requirement by payers and regulators for more real world data. One of the biggest factors impacting drug development is patient recruitment and retention. A new and innovative approach to conducting clinical trials is needed, and we have shown how patients can be enabled to measure clinical outcomes objectively and remotely while going about their daily lives. To obtain all the outcome measures required by a protocol, multiple devices may be needed, and we have shown how that can be achieved, while retaining full data privacy and security. Data collection without integration has a limited usefulness, so it was important to show how de-identified data collected through mobile devices can be (re)-integrated with the full set of clinical data on the patient in a secure environment in real time. We think there is huge potential in this approach to transform the way we monitor clinical trials and improve the quality of patient data. Data collected in this way are more objective and have a more transparent audit trail than more traditional clinical outcome assessment instruments.

W 46

Proof of Concept for the Development of Digital Biomarker using Raw Actigraphy Data from a Wrist Wearable Device

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Keywords: Actigraphy, digital biomarker, wearable devices

Method: Actigraphy data was gathered from a subject over the course of ~18hrs. The measurement period contained 7 teeth brushing events. A digital fingerprint for was developed and tested using 4 of these events and finally evaluated using the remaining 3 unseen events.

Objective: This poster reports the results of a proof of concept project developed by ICON Plc's Innovation Team for the development of a digital biomarker for identifying periods of teeth brushing activity from raw 100Hz Actigraphy data.

Result: When considering raw actigraphy data, there is very little value in an individual row of data (the actual accelerometer results for an individual moment in time) – the value comes from considering the pattern or relative change in the data over a period of time, an epoch. Another important consideration is the variation and duration of the event itself. A rolling 1 minute epoch has been selected for this project.

The raw data for each row was summarised into a single figure value, the vector magnitude for the tri-axial accelerometer values, along with the quadrant direction of the vector.

When rolling the raw data up into 1 minute epochs, a number of summary statistics were calculated, along with some descriptive parameters about the pattern of the vector magnitude – such as smoothed peaks per second and average period of peaks. A digital fingerprint was derived that most closed matched the 4 training events.

A function was defined which calculates the similarity of a 1 minute epoch to the fingerprint and was calibrated on the training events.

Whilst it was possible to obtain a very good fit on the 4 training events used to define the digital fingerprint – it proved difficult to obtain similar levels of accuracy (and particularly specificity) when evaluated on the 3 unseen events.

The limiting factor is a combination of the small number of events to develop a fingerprint from and the degree of variation between all 7 of the events, due to the largely stochastic nature of a teeth brushing event.

A final evaluation test was performed on an additional set of data containing 2 events gathered from a different subject. When evaluated on this dataset, no sufficiently matching patterns were found. Closer investigation showed that the pattern for the new subject, whilst similar, was outside of the similarity bounds defined by the test events.

Conclusion: The raw data collected by actigraphy devices can contain activity patterns not currently captured by existing validated algorithms.

With a sufficient amount of labelled data (i.e. where time periods with the event of interest occurring are marked) it is possible to derive a digital biomarker to measure when and how quantify the number of events occurred.

The quantity of data required to build a robust algorithm will depend on the variance in the pattern between individual events and from subject to subject.

Notwithstanding the limitations in evaluation performance, the project demonstrated that it is possible to derive a new digital biomarker from raw actigraphy data using a small training set.

The following individuals collaborated to develop this abstract: Louis Smith MSc, Data Science Manager, ICON; Marie McCarthy MSc, MBA, Director of Product Innovation, ICON; Michael Philips PhD, Director of Product Innovation, ICON; Wilhelm Muehlhausen DVM, VP Head of Innovation ICON

W 47

Testing for Bioequivalence in Higher-Order Crossover Designs: Two-at-a-Time Principle Versus Pooled ANOVA

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Keywords: Analysis of Variance (ANOVA), Bioequivalence, crossover design, two-at-a-time principle

Method: Empirical data from three-way crossover bioequivalence studies were examined using 1) the two-at-a-time principle and 2) a pooled approach using one ANOVA. Simulations will also be performed to control and compare the type I and II errors resulting from both methods of analyses.

Objective: The objective of this research is to determine which method of statistical analysis is more appropriate to conclude bioequivalence in higher-order crossover studies.

Result: Statistical results for the pharmacokinetic parameters AUC and Cmax were generated using the MIXED procedure in SAS©. The Test/Reference ratios and their associated 90% confidence intervals were estimated using 1) the two-at-a-time principle, where each Test formulation was compared to the Reference formulation in two separate incomplete block design ANOVAs, and 2) the pooled ANOVA where data from all three products were analyzed using one ANOVA. Analysis of empirical data showed that one method can pass bioequivalence criteria whereas the other method can fail bioequivalence criteria. This is mainly as result of 1) artificial increase in sample size using a pooled ANOVA approach to compare each of two Test formulations to a Reference, and 2) non-homogeneity of variances and different point estimates across formulations.

Conclusion: The method of statistical analysis of higher-order crossover studies can affect the bioequivalence conclusions of each formulation being tested. Empirical results show that using a two-at-a-time principle or a pooled ANOVA approach may produce different bioequivalence conclusions for the targeted comparison owing to the influence of the other formulations on those results. Simulations where type I and II errors are controlled will show which method of analysis produces less bias and more accurate bioequivalence conclusions.

W 48

Regulatory Turnaround Makes India an Increasingly Attractive Location for Clinical Research

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Keywords: Changing regulatory environment in India, clinical trials in India

Method: Various successful advocacy approaches have been implemented in India, resulting in improved clinical trial regulations due to broader stakeholder involvement, engagement with professional and industry associations, discussions on operational challenges and policy matters, and media education.

Objective: This poster will describe recent changes in the regulatory environment for clinical trials in India, highlighting recent improvements and lessons learned.

Result: Today, India has 17% of the world's population and 20% of the global disease burden (the highest in the world). In common with other emerging markets, India faces a 'triple burden' of communicable disease, non-communicable disease and socio-behavioral illness. Despite this unmet medical need, less than 1.4% of global clinical trials take place in India (source: www.clinicaltrials.gov).

As India emerges from a challenging period in its regulatory environment, the country is poised to become an increasingly attractive location for clinical research. This followed a period of decline in clinical research activity in 2013 – 2014 in India as a result of negative activism, sensational media reporting and constant scrutiny of the regulators by parliament and the judiciary which led to a slew of new regulations, guidelines and orders. While the intent of these regulations was to ensure patient safety and data integrity, they were issued without appropriate stakeholder consultation or operational guidance.

Regulators also spent significant time responding to queries from the court and parliament, impacting their ability to process new drug and clinical trial applications in a timely fashion. The resulting long, unpredictable timelines, coupled with new regulations, resulted in a decline in clinical research in India by commercial organizations, academic institutions and individual investigators. Patients, who

were denied an opportunity to participate in clinical trials, were the worst affected stakeholders of clinical research process.

Conclusion: The future for Indian clinical trials looks promising. As a result of consistent advocacy and ongoing dialogue with regulatory and policy makers, there has been a significant change in the regulatory environment.

Lessons learned include the importance of supporting responsible and ethical research through:
- Broader stakeholder involvement
- Advocacy on operational challenges and policy matters
- Actively providing feedback to regulators
- Engaging with industry associations, such as the Organization of Pharmaceutical Producers of India (OPPI), Confederation of Indian Industries (CII) Federation of Indian Chambers of Commerce and Industries (FICCI) and professional associations like Indian Society for Clinical Research (ISCR)
- Active engagement in media education and awareness

All these elements have had a positive impact, culminating in a promise from India's Drug Controller General Dr. G.N. Singh that his goal involved "streamlining regulatory procedures without compromising patient safety." (source: http://www.cdsco.nic.in/writereaddata/DCGI%20Message(1).pdf) Indian regulators have now adopted a consultative approach, and are committed to creating a more rational and scientific framework for clinical trials in India. Investments are being made to strengthen the regulatory infrastructure, including training of regulatory personnel, leading to shorter timelines for clinical trial approvals. Balanced compensation guidelines are also in place.

The approach of the regulators is more collaborative and open and they have repeatedly assured stakeholders of their commitment to bringing clinical research back on track in India. There are also indications of regulatory capacity building being taken seriously where, there will be an opportunity for industry and academia to partner with the regulators. These ongoing efforts continue to shape the regulatory environment through dialogue and collaboration.

W 49

Integrated Solution to Improve Eligibility Fraction and Time Factor in Patient Recruitment for Clinical Trials

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Keywords: Clinical trial, patient recruitment

Method: Studied the survey on traditional methods employed for patient recruitment and impact they have on clinical trials. Evaluated key strategies and solutions proposed to reduce recruitment time and improve eligibility fraction.

Objective: Discuss an integrated solution that brings together recruiter and sources to contribute collectively towards patient recruitment and key challenges in standing up such a system.

Result: Majority (nearly 86%) of clinical trials conducted in the United States fail to enrol subjects within contract period despite of many efforts. Too small subject pool per site,limited site capabilities and lack of patient awareness are potential factors for such failures. This demands a collaborative approach amongst research sites and patients to maximize subject pool in time and cost-effective manner.

Conclusion: Based on the survey analysis, it demands an intelligent system which integrates different sites, providers and patients to form a clinical trial community. The objective of such system is to meet enrolment goals by transforming patient information systems into clinical trial sensing nodes. IHE RM profile is a step forward to automate the search of appropriate subjects so we can enhance it to build such a smart system.

A central hub shall host several clinical trial domains comprising of Patient Recruiters (Recruitment firms,CRO,etc.) and Patient Information Sources (EHR/PHR,etc.). Each recruiter configures domain with the eligibility criteria. Once domain is formed, recruiter triggers a federated search on the subscribed sources. The hub reconciles list of consented patients whose health records match the trial requirements. Besides, patient sources can self-trigger a search for matching new patients to trials notifying respective recruiters. Additionally, domains can serve as platforms for communication, query resolution, advertisement, and patient education. Collaborative approach for patient recruitment facilitates focused search improving enrolment fraction. It also functions as a channel for targeted advertisements and patient education improving patient awareness. Effectiveness of above solution shall multiply as and when more number of recruiters and patient information sources register to hub subscribing for clinical trials. This would ultimately facilitate selection of diverse range of patients best-suited for the trial in a reduced period of time.

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Predicting Future State and Business Drivers of Safety System Upgrades based on Safety Database Upgrade and Industry Trends

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Keywords: Business case, future predictions, pharmacovigilance, safety system, trends, upgrade

Method: The industry drivers study was conducted over the last 10 years, from Jan. 2005-Dec. 2015, through direct and indirect involvement in safety system business cases, assessments and upgrades for over 25 global large/medium/small pharmaceutical and biotechnology companies.

Objective: The objective of this abstract is to identify and understand the significance of current business drivers and costs behind PV system upgrades and to critically think about how industry trends will impact these in the near future.

Result: During the years of study, quantitative data was collected on companies' business case for upgrade; previous, new, and planned safety systems and versions; desired system functionality; and components and the costs in terms of both financial costs and resourcing demands on the organization associated with these elements.

The data revealed the following drivers to upgrade safety systems:
- Regulatory compliance including compliance with new regulations, regulatory reporting capabilities, and increasing resourcing demands required to meet changing regulations

- Business requirements including business process harmonization, availability of custom extensions, need for analytics platforms, and system integrations
- Technical requirements including reusable implementation assets, technical support and compatibility, and multitenancy
- Business situations including business operating models, total cost of ownership, global single safety database, and resourcing needs

The data revealed the following drivers of upgrade costs:
- Current state of safety system(s) including the volume and complexity of existing systems and data
- User base, including the extent of global reach and the volume and complexity of users
- Implementation resources including the extent of the update, timeline, and the volume and complexity of integrations and customizations

The data suggests the following industry trends
- Changes in healthcare demographics, access, and treatment methods is increasing the volume and sources of safety data
- Growing consumer needs and the need to improve adverse event case acquisition is causing a growth in system upgrade market size
- Managing the increasingly complex balance between cost and regulatory pressures is causing a shift in the ownership and oversight of safety systems

The analysis confirmed that commonalities exist across the PV industry related to the drivers to upgrade and drivers of cost.

Conclusion: The study concluded that industry trends are disrupting the current balance of safety system upgrade drivers and cost. As safety upgrade costs are growing disproportionally to drivers, upgrade approaches will shift as the incremental value of the upgrade decreases. Implications to the drivers of safety system upgrades include:
- Regulatory reporting capabilities will increase in significance, as increasing emphasis on patient safety will require life sciences companies to acquire and perfect additional regulatory reporting capabilities beyond the traditional methods of capturing and managing safety data
- Multitenancy will increase in significance because this functionality will be favored for its versatility and potential to reduce costs as well as for its potential to leverage information across organizations
- Need for analytics platforms will increase in significance as life sciences organizations look to increase the value obtained from system upgrades and accommodate a higher volume of reported AEs/SAEs
- Total cost of ownership will increase in significance because life sciences organizations will seek out more cost effective system implementation and maintenance options as upgrades become more expensive and less valuable

Implications to the costs of safety system upgrades include:
- Volume and complexity of existing databases will increase in significance as regulatory pressures rise
- Volume of complexity of data will increase in significance as more adverse events are reported and new AE/SAE reporting technologies are leveraged
- Extent of global reach will increase in significance as consolidation pushes the global boundaries of many life sciences companies
- Volume and complexity of users will increase in significance with the shift to patient-centered care and the development of new technology for AE capture
- Volume and complexity of customizations will increase in significance as governance and objectives within a life sciences' organization change

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Visualizing Patients' ADaM Data via SAS and R

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Keywords: ADaM, CDISC, Graph, R, SAS

Method: We used SAS to create the datasets and graphs during the time of the RTQ. As hindsight, we realized R might do a better job and create the graphs easily. Therefore, this poster is going to show using SAS and R separately and the pros and cons of each method.

Objective: This poster intends to share our experience on creating an ADaM dataset and some graphs for an FDA RTQ question. The challenge was, how to show the patients' concurrent medications in parallel with dosing information and adverse event while those information are scattered in separate ADaM datasets.

Result: The quantitative data was in separate CDISC ADaM datasets: ADCM, ADAE, ADLB, ADEX and ADSL. The intent is to see if there is any trend between patients calcium supplement intake and their dosing reduction and IPTH lab results. The request is particularly challenging for programming when the patients take several kinds of calcium supplements, and when there are overlaps between the end date of one supplement with the next one. We did our programming in SAS during the time of RTQ. Right afterwards, afterwards, I attended an AMGEN internal conference and got inspired in two aspects: 1. We could use an alternative data step in SAS to elegantly combine different ADaM datasets to show the patients' various data at one point of time. 2. I also attended an introductory R talk and found out that R offers a dplyr package to manipulate data. It could also be the right tool to visualize the data and show the trend much more easily than SAS. Therefore, the different strategies will be explored. In terms of data processing, I will compare SAS proc transpose with dplyr in R studio. My hypothesis is R will have a lot of advantages over SAS in terms of programming time and efficiency.

Conclusion: After the different alternatives are tried out, it's concluded that R (dplyr) works more efficiently in transposing the data and putting them together for visualizing. It offers an excellent alternative tool for dealing with RTQ questions. If it can't be used for submission, at least it could be helpful for statisticians in validating SAS results.